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(21) International Application Number: PCT/EP99/09660 (22) International Filing Date: 7 December 1999 (07.12.99) (30) Priority Data: 09/206,601 7 December 1998 (07.12.98) US 60/111,255 7 December 1998 (07.12.98) US (71) Applicant (for all designated States except US): SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES S.A. [FR/FR]; 51-53, rue du Docteur Blanche, F-75016 Paris (FR). (72) Inventor; and (75) Inventor/Applicant (for US only): DONG, Zheng, Xin [CN/US]; 40 Angelica Drive, Framingham, MA 01701 (US). (74) Agent: LUNT, Mark, George, Francis; Dibb Lupton Alsop, Fountain Precinct, Balm Green, Sheffield S1 1RZ (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: ANALOGUES OF GLP-1 (57) Abstract <p>The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.</p>			

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ANALOGUES OF GLP-1Background of the Invention

5 The present invention is directed to peptide analogues of glucagon-like peptide-1, the pharmaceutically-acceptable salts thereof, to methods of using such analogues to treat mammals and to pharmaceutical compositions useful therefor comprising said analogues.

10 Glucagon-like peptide-1 (7-36) amide (GLP-1) is synthesized in the intestinal L-cells by tissue-specific post-translational processing of the glucagon precursor preproglucagon (Varndell, J.M., et al., *J. Histochem Cytochem*, 1985;33:1080-6) and is released into the circulation in response to a meal. The plasma concentration of GLP-1 rises from a fasting level of approximately 15 pmol/L to a peak postprandial level of 40 pmol/L. It has been demonstrated that, for 15 a given rise in plasma glucose concentration, the increase in plasma insulin is approximately threefold greater when glucose is administered orally compared with intravenously (Kreymann, B., et al., *Lancet* 1987;2, 1300-4). This alimentary enhancement of insulin release, known as the incretin effect, is primarily humoral and GLP-1 is now thought to be the most potent physiological incretin in humans.

20 In addition to the insulinotropic effect, GLP-1 suppresses glucagon secretion, delays gastric emptying (Wettergren A., et al., *Dig Dis Sci* 1993;38:665-73) and may enhance peripheral glucose disposal (D'Alessio, D.A. et al., *J. Clin Invest* 1994;93:2293-6).

25 In 1994, the therapeutic potential of GLP-1 was suggested following the observation that a single subcutaneous (s/c) dose of GLP-1 could completely normalize postprandial glucose levels in patients with non-insulin-dependent diabetes mellitus (NIDDM) (Gutniak, M.K., et al., *Diabetes Care* 1994;17:1039-44). This effect was thought to be mediated both by increased insulin release and by a reduction in glucagon secretion. Furthermore, an intravenous infusion of GLP-1 has 30 been shown to delay postprandial gastric emptying in patients with NIDDM (Williams, B., et al., *J. Clin Endo Metab* 1996;81:327-32). Unlike sulphonylureas, the insulinotropic action of GLP-1 is dependent on plasma glucose concentration (Holz, G.G. 4th, et al., *Nature* 1993;361:362-5). Thus, the loss of GLP-1-mediated insulin release at low plasma glucose concentration protects against severe

hypoglycemia. This combination of actions gives GLP-1 unique potential therapeutic advantages over other agents currently used to treat NIDDM.

Numerous studies have shown that when given to healthy subjects, GLP-1 potently influences glycemic levels as well as insulin and glucagon concentrations

5 (Orskov, C, Diabetologia 35:701-711, 1992; Holst, J.J., et al., Potential of GLP-1 in diabetes management in Glucagon III, Handbook of Experimental Pharmacology, Lefevbre PJ, Ed. Berlin, Springer Verlag, 1996, p. 311-326), effects which are glucose dependent (Kreymann, B., et al., Lancet ii: 1300-1304, 1987; Weir, G.C., et al., Diabetes 38:338-342, 1989). Moreover, it is also effective in patients with

10 diabetes (Gutniak, M., N. Engl J Med 226:1316-1322, 1992; Nathan, D.M., et al., Diabetes Care 15:270-276, 1992), normalizing blood glucose levels in type 2 diabetic subjects (Nauck, M.A., et al., Diabetologia 36:741-744, 1993), and improving glycemic control in type 1 patients (Creutzfeldt, W.O., et al., Diabetes Care 19:580-586, 1996), raising the possibility of its use as a therapeutic agent.

15 GLP-1 is, however, metabolically unstable, having a plasma half-life ($t_{1/2}$) of only 1-2 min *in vivo*. Exogenously administered GLP-1 is also rapidly degraded (Deacon, C.F., et al., Diabetes 44:1126-1131, 1995). This metabolic instability limits the therapeutic potential of native GLP-1. Hence, there is a need for GLP-1 analogues that are more active or are more metabolically stable than native GLP-1.

20 Summary of the Invention

In one aspect, the present invention is directed to a compound of formula (I),

(R²R³)-A⁷-A⁸-A⁹-A¹⁰-A¹¹-A¹²-A¹³-A¹⁴-A¹⁵-A¹⁶-A¹⁷-A¹⁸-A¹⁹-A²⁰-A²¹-A²²-A²³-A²⁴-A²⁵-A²⁶-A²⁷-A²⁸-A²⁹-A³⁰-A³¹-A³²-A³³-A³⁴-A³⁵-A³⁶-A³⁷-A³⁸-A³⁹-R¹,

25 (I)

wherein

A⁷ is L-His, Ura, Paa, Pta, Amp, Tma-His, des-amino-His, or deleted;

A⁸ is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;

A⁹ is Glu, N-Me-Glu, N-Me-Asp or Asp;

30 A¹⁰ is Gly, Acc, β -Ala or Aib;

A¹¹ is Thr or Ser;

A¹² is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, β -Nal, Cha, Trp or X¹-Phe;

A¹³ is Thr or Ser;

A¹⁴ is Ser or Aib;

A¹⁵ is Asp or Glu;

A¹⁶ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;

A¹⁷ is Ser or Thr;

A¹⁸ is Ser or Thr;

5 A¹⁹ is Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β -Nal or X¹-Phe;

A²⁰ is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X¹-Phe;

A²¹ is Glu or Asp;

A²² is Gly, Acc, β -Ala, Glu or Aib;

A²³ is Gln, Asp, Asn or Glu;

10 A²⁴ is Ala, Aib, Val, Abu, Tle or Acc;

A²⁵ is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A²⁶ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);

15 A²⁷ is Glu Asp, Leu, Aib or Lys;

A²⁸ is Phe, Pal, β -Nal, X¹-Phe, Aic, Acc, Aib, Cha or Trp;

A²⁹ is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;

A³⁰ is Ala, Aib or Acc;

A³¹ is Trp, β -Nal, 3-Pal, 4-Pal, Phe, Acc, Aib or Cha;

20 A³² is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X¹-Phe or Ala;

A³³ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, Lys or X¹-Phe;

A³⁴ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O);

A³⁵ is Gly, β -Ala, D-Ala, Gaba, Ava, HN-(CH₂)_m-C(O), Aib, Acc or a D-amino acid;

25 A³⁶ is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), HN-CH((CH₂)_e-X³)-C(O) or deleted;

A³⁷ is Gly, β -Ala, Gaba, Ava, Aib, Acc, Ado, Arg, Asp, Aun, Aec, HN-(CH₂)_m-C(O), HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), a D-amino acid, or deleted;

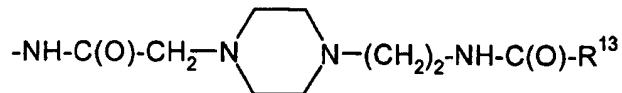
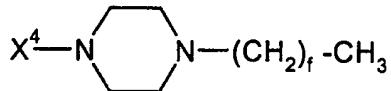
A³⁸ is D- or L-Lys, D- or L-Arg, D- or L-hArg, D- or L-Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), HN-CH((CH₂)_e-X³)-C(O) Ava, Ado, Aec or deleted;

30 A³⁹ is D- or L-Lys, D- or L-Arg, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), Ava, Ado, or Aec;

X¹ for each occurrence is independently selected from the group consisting of (C₁-C₆)alkyl, OH and halo;

R^1 is OH, NH₂, (C₁-C₃₀)alkoxy, or NH-X²-CH₂-Z⁰, wherein X² is a (C₁-C₁₂)hydrocarbon moiety, and Z⁰ is H, OH, CO₂H or CONH₂;

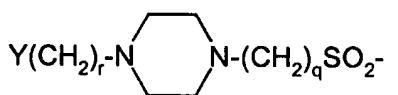
X^3 is



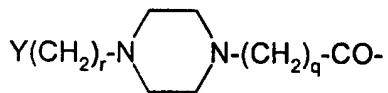
5 or -C(O)-NHR¹², wherein X⁴ is, independently for each occurrence, -C(O)-, -NH-C(O)- or -CH₂-; and wherein f is, independently for each occurrence, an integer from 1 to 29 inclusive;

each of R² and R³ is independently selected from the group consisting of H, (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-C₃₀)alkyl, 10 hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl, and

hydroxynaphthyl(C₁-C₃₀)alkyl; or one of R² and R³ is (CH₃)₂-N-C=N(CH₃)₂, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, C(O)X⁵,



, or



; wherein Y is H, OH or NH₂; r is 0 to 4; q is 0 to 4;

and X⁵ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl,

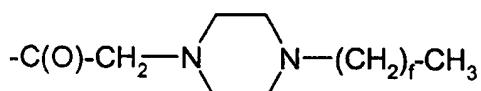
15 hydroxy(C₁-C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl or hydroxynaphthyl(C₁-C₃₀)alkyl;

e is, independently for each occurrence, an integer from 1 to 4 inclusive;

m is, independently for each occurrence, an integer from 5 to 24 inclusive;

n is, independently for each occurrence, an integer from 1 to 5, inclusive;

20 each of R¹⁰ and R¹¹ is, independently for each occurrence, H, (C₁-C₃₀)alkyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl, -C((NH)(NH₂)) or



; and

R¹² and R¹³ each is, independently for each occurrence, (C₁-C₃₀)alkyl;

provided that:

when A^7 is Ura, Paa or Pta, then R^2 and R^3 are deleted;

when R^{10} is $(\text{C}_1\text{-C}_{30})\text{acyl}$, $(\text{C}_1\text{-C}_{30})\text{alkylsulfonyl}$, $-\text{C}((\text{NH})(\text{NH}_2))$ or



, then R^{11} is H or $(\text{C}_1\text{-C}_{30})\text{alkyl}$;

- 5 (i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH;
- (ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH wherein a single position has been substituted by Ala;
- (iii) a compound of formula (I) is not $(\text{Arg}^{26,34}, \text{Lys}^{38})\text{hGLP-1(7-38)-E}$, $(\text{Lys}^{26}(\text{N-alkanoyl}))\text{hGLP-1(7-36, -37 or -38)-E}$, $(\text{Lys}^{34}(\text{N-alkanoyl}))\text{hGLP-1(7-36, -37 or -38)-E}$, $(\text{Lys}^{26,34}\text{-bis}(\text{N-alkanoyl}))\text{hGLP-1(7-36, -37 or -38)-E}$, $(\text{Arg}^{26}, \text{Lys}^{34}(\text{N-alkanoyl}))\text{hGLP-1(8-36, -37 or -38)-E}$, $(\text{Arg}^{26,34}, \text{Lys}^{36}(\text{N-alkanoyl}))\text{hGLP-1(7-36, -37 or -38)-E}$ or $(\text{Arg}^{26,34}, \text{Lys}^{38}(\text{N-alkanoyl}))\text{hGLP-1(7-38)-E}$, wherein E is -OH or -NH₂;
- 10 (iv) a compound of formula (I) is not $\text{Z}^1\text{-hGLP-1(7-36, -37 or -38)-OH}$, $\text{Z}^1\text{-hGLP-1(7-36, -37 or -38)-NH}_2$, wherein Z^1 is selected from the group consisting of:
- (a) $(\text{Arg}^{26}), (\text{Arg}^{34}), (\text{Arg}^{26,34}), (\text{Lys}^{36}), (\text{Arg}^{26}, \text{Lys}^{36}), (\text{Arg}^{34}, \text{Lys}^{36}), (\text{D-Lys}^{36}), (\text{Arg}^{36}), (\text{D-Arg}^{36}), (\text{Arg}^{26,34}, \text{Lys}^{36})$ or $(\text{Arg}^{26,36}, \text{Lys}^{34})$;
- (b) (Asp^{21}) ;
- (c) at least one of (Aib^8) , (D-Ala^8) and (Asp^9) ; and
- 20 (d) $(\text{Tyr}^7), (\text{N-acyl-His}^7), (\text{N-alkyl-His}^7), (\text{N-acyl-D-His}^7)$ or (N-alkyl-D-His^7) ;
- (v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and
- (vi) a compound of formula (I) is not $(\text{N-Me-Ala}^8)\text{hGLP-1(8-36 or -37)}, (\text{Glu}^{15})\text{hGLP-1(7-36 or -37)}, (\text{Asp}^{21})\text{hGLP-1(7-36 or -37)}$ or $(\text{Phe}^{31})\text{hGLP-1(7-36 or -37)}$
- 25 or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing compound is where A^{11} is Thr; A^{13} is Thr; A^{15} is Asp; A^{17} is Ser; A^{18} is Ser or Lys; A^{21} is Glu; A^{23} is Gln or Glu; A^{27} is Glu, Leu, Aib or Lys; and A^{31} is Trp, Phe or β -Nal; or a pharmaceutically acceptable salt thereof.

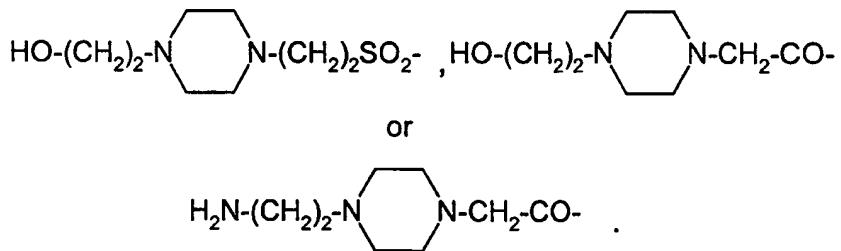
- 30 A preferred group of compounds of the immediately foregoing group of compounds is where A^9 is Glu, N-Me-Glu or N-Me-Asp; A^{12} is Phe, Acc, β -Nal or Aic; A^{16} is Val, Acc or Aib; A^{19} is Tyr or β -Nal; A^{20} is Leu, Acc or Cha; A^{24} is Ala, Aib

or Acc; A²⁵ is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹)-C(O) or HN-CH((CH₂)_e-X³)-C(O); A²⁸ is Phe or β -Nal; A²⁹ is Ile or Acc; A³⁰ is Ala or Aib; A³² is Leu, Acc or Cha; and A³³ is Val, Lys or Acc; or a pharmaceutically acceptable salt thereof.

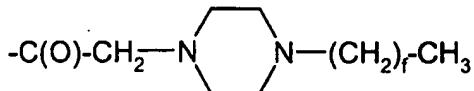
5 A preferred group of compounds of the immediately foregoing group of compounds is where A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly; A¹² is Phe, β -Nal, A6c or A5c; A¹⁶ is Val, A6c or A5c; A²⁰ is Leu, A6c, A5c or Cha; A²² is Gly, β -Ala, Glu or Aib; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c or A5c; A³² is Leu, A6c, A5c or Cha; A³³ is Val, Lys, A6c or A5c; A³⁵ is Aib, β -Ala, Ado, 10 A6c, A5c, D-Arg or Gly; and A³⁷ is Gly, Aib, β -Ala, Ado, D-Ala Ava, Asp, Aun, D-Asp, D-Arg, Aec, HN-CH((CH₂)_n-N(R¹⁰R¹¹)-C(O) or deleted; or a pharmaceutically acceptable salt thereof.

15 A preferred group of compounds of the immediately foregoing group of compounds is where X⁴ for each occurrence is -C(O)-; and R¹ is OH or NH₂; or a pharmaceutically acceptable salt thereof.

A preferred group of compounds of the immediately foregoing group of compounds or a pharmaceutically acceptable salt thereof is where R² is H and R³ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl,

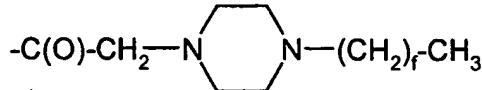


20 A preferred compound of the formula (I) is where A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly; A¹² is Phe, β -Nal A6c or A5c; A¹⁶ is Val, A6c or A5c; A²⁰ is Leu, A6c, A5c or Cha; A²² is Gly, β -Ala, Glu or Aib; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c or A5c; A³² is Leu, A6c, A5c or Cha; A³³ is Val, Lys, A6c or A5c; A³⁵ is Aib, β -Ala, Ado, A6c, A5c D-Arg or Gly; and A³⁷ is Gly, Aib, β -Ala, Ado, D-Ala, Ava, Asp, Aun, D-Asp, D-Arg, Aec, HN-CH((CH₂)_n-N(R¹⁰R¹¹)-C(O) or deleted; X⁴ for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; R¹ is OH or NH₂; R¹⁰ is (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl or



, and R¹¹ is H; or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing compounds is where R¹⁰ is (C₄-



C₂₀)acyl, (C₄-C₂₀)alkylsulfonyl or

5 pharmaceutically acceptable salt thereof.

A more preferred compound of formula (I) is where said compound is of the formula:

(Aib^{8,35})hGLP-1(7-36)NH₂,

((N_o-HEPES-His)⁷, Aib^{8,35})hGLP-1(7-36)NH₂,

10 ((N_o-HEPA-His)⁷, Aib^{8,35})hGLP-1(7-36)NH₂,

(Aib⁸, β -Ala³⁵)hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N_c-tetradecanoyl))hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg²⁶, Lys³⁴(N_c-tetradecanoyl))hGLP-1(7-36)NH₂,

(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N_c-tetradecanoyl))hGLP-1(7-38)NH₂,

15 (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N_c-decanoyl))hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N_c-dodecanesulfonyl))hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N_c-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-(4-tetradecyl-piperazine)))hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-tetradecylamino))hGLP-1(7-36)NH₂,

20 (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N_c-tetradecanoyl), β -Ala³⁷)hGLP-1(7-37)-OH or

(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N_c-tetradecanoyl))hGLP-1(7-36)-OH,

or a pharmaceutically acceptable salt thereof.

More preferred of the immediately foregoing group of compounds is a compound of the formula:

25 (Aib^{8,35})hGLP-1(7-36)NH₂,

(Aib⁸, β -Ala³⁵)hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg²⁶, Lys³⁴(N_c-tetradecanoyl))hGLP-1(7-36)NH₂,

(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N_c-tetradecanoyl))hGLP-1(7-38)NH₂,

(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N_c-decanoyl))hGLP-1(7-36)NH₂, or

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β -Ala³⁷)hGLP-1(7-37) -OH, or a pharmaceutically acceptable salt thereof.

Another more preferred compound of formula (I) is where said compound is of the formula:

- 5 (Aib^{8,35}, A6c³²)hGLP-1(7-36)NH₂;
- (Aib^{8,35}, Glu²³)hGLP-1(7-36)NH₂;
- (Aib^{8,24,35})hGLP-1(7-36)NH₂;
- (Aib^{8,35}, Glu²³, A6c³²)hGLP-1(7-36)NH₂;
- (Aib⁸, Glu²³, β -Ala³⁵)hGLP-1(7-36)NH₂;
- 10 (Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH₂;
- (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂;
- (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl))hGLP-1(7-36)OH;
- (Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-decanoyl))hGLP-1(7-36)OH;
- (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^ε-Aec-decanoyl))hGLP-1(7-36)NH₂;
- 15 (Aib^{8,35}, Arg^{26,34}, Ava³⁷, Ado³⁸)hGLP-1(7-38)NH₂;
- (Aib^{8,35}, Arg^{26,34}, Asp³⁷, Ava³⁸, Ado³⁹)hGLP-1(7-39)NH₂;
- (Aib^{8,35}, Arg^{26,34}, Aun³⁷)hGLP-1(7-37)NH₂;
- (Aib^{8,17,35},)hGLP-1(7-36)NH₂;
- (Aib⁸, Arg^{26,34}, β -Ala³⁵, D-Asp³⁷, Ava³⁸, Aun³⁹)hGLP-1(7-39)NH₂;
- 20 (Gly⁸, β -Ala³⁵)hGLP-1(7-36)NH₂;
- (Ser⁸, β -Ala³⁵)hGLP-1(7-36)NH₂;
- (Aib⁸, Glu^{22,23}, β -Ala³⁵)hGLP-1(7-36)NH₂;
- (Gly⁸, Aib³⁵)hGLP-1(7-36)NH₂;
- (Aib⁸, Lys¹⁸, β -Ala³⁵)hGLP-1(7-36)NH₂;
- 25 (Aib⁸, Leu²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂;
- (Aib⁸, Lys³³, β -Ala³⁵)hGLP-1(7-36)NH₂;
- (Aib⁸, Lys¹⁸, Leu²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂;
- (Aib⁸, D-Arg³⁶)hGLP-1(7-36)NH₂;
- (Aib⁸, β -Ala³⁵, D-Arg³⁷)hGLP-1(7-37)NH₂;
- 30 (Aib^{8,27}, β -Ala³⁵)hGLP-1(7-36)NH₂;
- (Aib^{8,27}, β -Ala^{35,37}, Arg³⁸)hGLP-1(7-38)NH₂;
- (Aib^{8,27}, β -Ala^{35,37}, Arg^{38,39})hGLP-1(7-39)NH₂;
- (Aib⁸, Lys^{18,27}, β -Ala³⁵)hGLP-1(7-36)NH₂;
- (Aib⁸, Lys²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, β -Ala³⁵, Arg³⁸)hGLP-1(7-38)NH₂;
(Aib⁸, Arg^{26,34}, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, D-Arg³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, β -Ala³⁵, Arg³⁷)hGLP-1(7-37)NH₂;
5 (Aib⁸, Phe³¹, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Phe³¹)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Nal³¹)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Nal^{28,31})hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Nal³¹)hGLP-1(7-36)NH₂;
10 (Aib^{8,35}, Arg^{26,34}, Phe³¹)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Nal^{19,31})hGLP-1(7-36)NH₂;
(Aib^{8,35}, Nal^{12,31})hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys³⁶(N^c-decanoyl))hGLP-1(7-36) NH₂;
(Aib^{8,35}, Arg³⁴, Lys²⁶(N^c-decanoyl))hGLP-1(7-36)NH₂;
15 (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-dodecanoyl))hGLP-1(7-36)NH₂;
(Aib⁸, β -Ala³⁵, Ser³⁷(O-decanoyl))hGLP1(7-37)-NH₂;
(Aib^{8,27}, β -Ala^{35,37}, Arg³⁸, Lys³⁹(N^c-octanoyl))hGLP-1(7-39)NH₂;
(Aib⁸, Arg^{28,34}, β -Ala³⁵, Lys³⁷(N^c-octanoyl))hGLP-1(7-37)NH₂;
20 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-decanoyl))hGLP-1(7-37)NH₂; or
or a pharmaceutically acceptable salt thereof.

Another more preferred compound of formula (I) is each of the compounds that are specifically enumerated hereinbelow in the Examples section of the present disclosure, or a pharmaceutically acceptable salt thereof.

25 In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

In yet another aspect, the present invention provides a method of eliciting
30 an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a method of treating a disease selected from the group consisting of Type I diabetes, Type II diabetes,

obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis, neurodegenerative disease, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, hypertension, and disorders wherein the

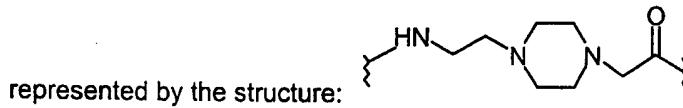
5 reduction of food intake is desired, in a subject in need thereof which comprises administering to said subject an effective amount of a compound of formula (I) as defined hereinabove or a pharmaceutically acceptable salt thereof. A preferred method of the immediately foregoing method is where the disease being treated is Type I diabetes or Type II diabetes.

10 With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is the side chain of an amino acid (e.g., CH₃ for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of (R²R³)-N-CH(R)-CO-, wherein R is a side chain of an amino acid and R² and R³ are as defined above, except when A⁷

15 is Ura, Paa or Pta, in which case R² and R³ are not present since Ura, Paa and Pta are considered here as des-amino amino acids. Amp, β -Nal, Nle, Cha, 3-Pal, 4-Pal and Aib are the abbreviations of the following α -amino acids: 4-amino-phenylalanine, β -(2-naphthyl)alanine, norleucine, cyclohexylalanine, β -(3-pyridinyl)alanine, β -(4-pyridinyl)alanine and α -aminoisobutyric acid, respectively.

20 Other amino acid definitions are: Ura is urocanic acid; Pta is (4-pyridylthio) acetic acid; Paa is *trans*-3-(3-pyridyl) acrylic acid; Tma-His is N,N-tetramethylamidino-histidine; N-Me-Ala is N-methyl-alanine; N-Me-Gly is N-methyl-glycine; N-Me-Glu is N-methyl-glutamic acid; Tle is *tert*-butylglycine; Abu is α -aminobutyric acid; Tba is *tert*-butylalanine; Orn is ornithine; Aib is α -aminoisobutyric acid; β -Ala is β -alanine;

25 Gaba is γ -aminobutyric acid; Ava is 5-aminovaleric acid; Ado is 12-aminododecanoic acid, Aic is 2-aminoindane-2-carboxylic acid; Aun is 11-aminoundecanoic acid; and Aec is 4-(2-aminoethyl)-1-carboxymethyl-piperazine,

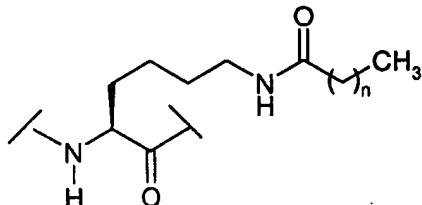


What is meant by Acc is an amino acid selected from the group of 1-amino-1-cyclopropanecarboxylic acid (A3c); 1-amino-1-cyclobutanecarboxylic acid (A4c); 1-amino-1-cyclopentanecarboxylic acid (A5c); 1-amino-1-cyclohexanecarboxylic acid (A6c); 1-amino-1-cycloheptanecarboxylic acid (A7c); 1-amino-1-

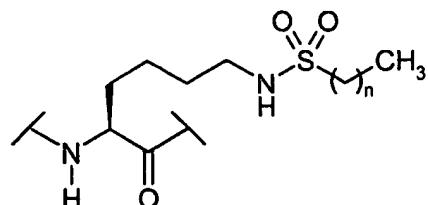
cyclooctanecarboxylic acid (A8c); and 1-amino-1-cyclononanecarboxylic acid (A9c).

In the above formula, hydroxyalkyl, hydroxyphenylalkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. COX⁵ stands for -C=O·X⁵. Examples of -C=O·X⁵ include, but are not limited to, acetyl and phenylpropionyl.

5 What is meant by Lys(N_n-alkanoyl) is represented by the following structure:

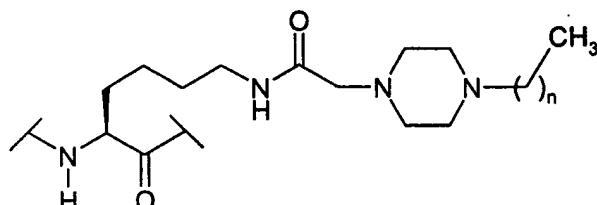


What is meant by Lys(N_n-alkylsulfonyl) is



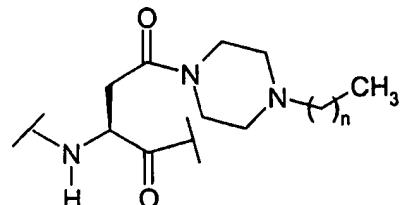
represented by the following structure: What

is meant by Lys(N_n-(2-(4-alkyl-1-piperazine)-acetyl)) is represented by the following

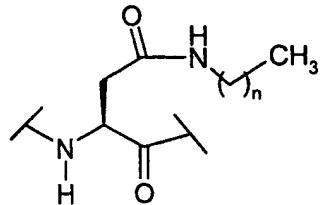


structure: What is meant by

10 Asp(1-(4-alkyl-piperazine)) is represented by the following

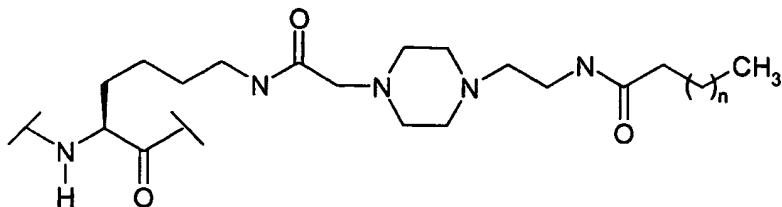


structure: What is meant by Asp(1-alkylamino)



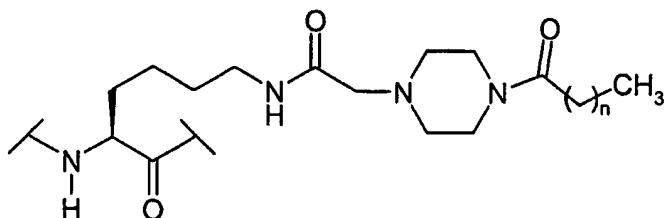
is represented by the following structure: What is

meant by Lys(N_n-Aec-alkanoyl) is represented by the structure:



The variable n

in the foregoing structures is 1-30. What is meant by Lys (N^ε-ace-alkanoyl) is represented by the structure:



5

The full names for other abbreviations used herein are as follows: Boc for t-butyloxycarbonyl, HF for hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl 10 uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc for acetic acid, TFA for trifluoroacetic acid, 2ClZ for 2-chlorobenzyloxycarbonyl, 2BrZ for 2-bromobenzyloxycarbonyl, OcHex for O-cyclohexyl, Fmoc for 9-fluorenylmethoxycarbonyl, HOBt for N-hydroxybenzotriazole and PAM resin for 4-hydroxymethylphenylacetamidomethyl resin.

15 The term "halo" encompasses fluoro, chloro, bromo and iodo

The term "(C₁-C₃₀)hydrocarbon moiety" encompasses alkyl, alkenyl and alkynyl, and in the case of alkenyl and alkynyl there are C₂-C₃₀.

A peptide of this invention is also denoted herein by another format, e.g., (A5c⁸)hGLP-1(7-36)NH₂, with the substituted amino acids from the natural sequence placed between the first set of parentheses (e.g., A5c⁸ for Ala⁸ in hGLP-1). The abbreviation GLP-1 means glucagon-like peptide-1; hGLP-1 means human glucagon-like peptide-1. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hGLP-1(7-36) is amino acids 7 through 36 of the peptide sequence for human GLP-1). The sequence for hGLP-

1(7-37) is listed in Mojsov, S., Int. J. Peptide Protein Res., 40, 1992, pp. 333-342. The designation "NH₂" in hGLP-1(7-36)NH₂ indicates that the C-terminus of the peptide is amidated. hGLP-1(7-36) means that the C-terminus is the free acid. In hGLP-1(7-38), residues in positions 37 and 38 are Gly and Arg, respectively.

5

Detailed Description

The peptides of this invention can be prepared by standard solid phase peptide synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The substituents R² and R³ of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C₁-C₃₀)alkyl, may be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C₁-C₃₀)hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COE¹, may be attached by coupling the free acid, e.g., E¹COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

When R¹ is NH-X²-CH₂-CONH₂, (i.e., Z⁰=CONH₂), the synthesis of the peptide starts with BocHN-X²-CH₂-COOH which is coupled to the MBHA resin. If R¹ is NH-X²-CH₂-COOH, (i.e., Z⁰=COOH) the synthesis of the peptide starts with Boc-HN-X²-CH₂-COOH which is coupled to PAM resin. For this particular step, 4 molar equivalents of Boc-HN-X²-COOH, HBTU and HOBT and 10 molar equivalents of DIEA are used. The coupling time is about 8 hours.

25

The protected amino acid 1-(N-tert-butoxycarbonyl-amino)-1-cyclohexane-carboxylic acid (Boc-A6c-OH) was synthesized as follows. 19.1 g (0.133 mol) of 1-amino-1-cyclohexanecarboxylic acid (Acros Organics, Fisher Scientific, Pittsburgh, PA) was dissolved in 200 ml of dioxane and 100 ml of water. To it was added 67 ml of 2N NaOH. The solution was cooled in an ice-water bath. 32.0 g (0.147 mol) of di-tert-butyl-dicarbonate was added to this solution. The reaction mixture was stirred overnight at room temperature. Dioxane was then removed under reduced pressure. 200 ml of ethyl acetate was added to the remaining aqueous solution. The mixture was cooled in an ice-water bath. The pH of the aqueous layer was adjusted to about 3 by adding 4N HCl. The organic layer was separated. The

aqueous layer was extracted with ethyl acetate (1 x 100 ml). The two organic layers were combined and washed with water (2 x 150 ml), dried over anhydrous MgSO₄, filtered, and concentrated to dryness under reduced pressure. The residue was recrystallized in ethyl acetate/hexanes. 9.2 g of the pure product was 5 obtained. 29% yield.

Boc-A5c-OH was synthesized in an analogous manner to that of Boc-A6c-OH. Other protected Acc amino acids can be prepared in an analogous manner by a person of ordinary skill in the art as enabled by the teachings herein.

In the synthesis of a GLP-1 analogue of this invention containing A5c, A6c 10 and/or Aib, the coupling time is 2 hrs. for these residues and the residue immediately following them. For the synthesis of (Tma-His⁷)hGLP-1(7-36)NH₂, HBTU (2 mmol) and DIEA (1.0 ml) in 4 ml DMF are used to react with the N-terminal free amine of the peptide-resin in the last coupling reaction; the coupling time is about 2 hours.

15 The substituents R² and R³ of the above generic formula can be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For example, alkyl groups, e.g., (C₁-C₃₀)alkyl, can be attached using reductive 20 alkylation. Hydroxyalkyl groups, e.g., (C₁-C₃₀)hydroxyalkyl, can also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COX¹, can be attached by coupling the free acid, e.g., X¹COOH, to the free amine of the N-terminal amino acid by mixing the completed 25 resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for about one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

A compound of the present invention can be tested for activity as a GLP-1 binding compound according to the following procedure.

Cell Culture:

30 RIN 5F rat insulinoma cells (ATCC-# CRL-2058, American Type Culture Collection, Manassas, VA), expressing the GLP-1 receptor, were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum, and maintained at about 37 °C in a humidified atmosphere of 5% CO₂/95% air.

Radioligand Binding:

Membranes were prepared for radioligand binding studies by

homogenization of the RIN cells in 20 ml of ice-cold 50 mM Tris-HCl with a Brinkman Polytron (Westbury, NY) (setting 6, 15 sec). The homogenates were washed twice by centrifugation (39,000 g / 10 min), and the final pellets were resuspended in 50 mM Tris-HCl, containing 2.5 mM MgCl₂, 0.1 mg/ml bacitracin
5 (Sigma Chemical, St. Louis, MO), and 0.1% BSA. For assay, aliquots (0.4 ml) were incubated with 0.05 nM (¹²⁵I)GLP-1(7-36) (~2200 Ci/mmol, New England Nuclear, Boston, MA), with and without 0.05 ml of unlabeled competing test peptides. After a 100 min incubation (25 °C), the bound (¹²⁵I)GLP-1(7-36) was separated from the free by rapid filtration through GF/C filters (Brandel,
10 Gaithersburg, MD), which had been previously soaked in 0.5% polyethyleneimine. The filters were then washed three times with 5 ml aliquots of ice-cold 50 mM Tris-HCl, and the bound radioactivity trapped on the filters was counted by gamma spectrometry (Wallac LKB, Gaithersburg, MD). Specific binding was defined as the total (¹²⁵I)GLP-1(7-36) bound minus that bound in the presence of 1000 nM
15 GLP1(7-36) (Bachem, Torrence, CA).

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic, or pamoic acid),
20 inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids). A typical method of making a salt of a peptide of the present invention is well known in the art and can be accomplished by standard methods of salt exchange. Accordingly, the TFA salt of a peptide of the
25 present invention (the TFA salt results from the purification of the peptide by using preparative HPLC, eluting with TFA containing buffer solutions) can be converted into another salt, such as an acetate salt by dissolving the peptide in a small amount of 0.25 N acetic acid aqueous solution. The resulting solution is applied to a semi-prep HPLC column (Zorbax, 300 SB, C-8). The column is eluted with (1)
30 0.1N ammonium acetate aqueous solution for 0.5 hrs., (2) 0.25N acetic acid aqueous solution for 0.5 hrs. and (3) a linear gradient (20% to 100% of solution B over 30 min.) at a flow rate of 4 ml/min (solution A is 0.25N acetic acid aqueous solution; solution B is 0.25N acetic acid in acetonitrile/water, 80:20). The fractions containing the peptide are collected and lyophilized to dryness.

As is well known to those skilled in the art, the known and potential uses of GLP-1 is varied and multitudinous (See, Todd, J.F., et al., Clinical Science, 1998, 95, pp. 325-329; and Todd, J.F. et al., European Journal of Clinical Investigation, 1997, 27, pp.533-536). Thus, the administration of the compounds of this invention for purposes of eliciting an agonist effect can have the same effects and uses as GLP-1 itself. These varied uses of GLP-1 may be summarized as follows, treatment of: Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system diseases, restenosis, neurodegenerative diseases, renal failure, congestive heart failure, nephrotic syndrome, cirrhosis, pulmonary edema, hypertension, and disorders wherein the reduction of food intake is desired. GLP-1 analogues of the present invention that elicit an antagonist effect from a subject can be used for treating the following: hypoglycemia and malabsorption syndrome associated with gastroectomy or small bowel resection.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of formula (I) in association with a pharmaceutically acceptable carrier.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. In general, an effective dosage for the activities of this invention is in the range of 1×10^{-7} to 200 mg/kg/day, preferably 1×10^{-4} to 100 mg/kg/day, which can be administered as a single dose or divided into multiple doses.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating

agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

5 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

10 Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, 15 for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

20 Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

25 Further, a compound of this invention can be administered in a sustained release composition such as those described in the following patents and patent applications. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. 30 U.S. Application No. 08/929,363 filed September 9, 1997, teaches polymeric sustained release compositions comprising a bioactive agent and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising a bioactive agent and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbable sustained release

compositions of a bioactive agent. U.S. Application No. 09/121,653 filed July 23, 1998, teaches a process for making microparticles comprising a therapeutic agent such as a peptide in an oil-in-water process. U.S. Application No. 09/131,472 filed August 10, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a phosphorylated polymer. U.S. Application No. 09/184,413 filed November 2, 1998, teaches complexes comprising a therapeutic agent such as a peptide and a polymer bearing a non-polymerizable lactone. The teachings of the foregoing patents and applications are incorporated herein by reference.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Also, all publications, patent applications, patents and other references mentioned herein are incorporated by reference.

The following examples describe synthetic methods for making a peptide of this invention, which methods are well-known to those skilled in the art. Other methods are also known to those skilled in the art. The examples are provided for the purpose of illustration and is not meant to limit the scope of the present invention in any manner.

Boc- β Ala-OH, Boc-D-Arg(Tos)-OH and Boc-D-Asp(OcHex) were purchased from Nova Biochem, San Diego, California. Boc-Aun-OH was purchased from Bachem, King of Prussia, PA. Boc-Ava-OH and Boc-Ado-OH were purchased from Chem-Impex International, Wood Dale, IL. Boc-Nal-OH was purchased from Synthetech, Inc. Albany, OR.

Example 1



The title peptide was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnolzer, et al., Int. J. Peptide Protein Res., 90:180 (1992). 4-methylbenzhydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.91 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem., LaJolla, CA) were used with the following side chain protection: Boc-Ala-OH, Boc-Arg(Tos)-OH, Boc-Asp(OcHex)-OH, Boc-Tyr(2BrZ)-OH, Boc-His(DNP)-OH, Boc-Val-OH, Boc-Leu-OH, Boc-Gly-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2ClZ)-OH, Boc-Thr(Bzl)-OH, Boc-Ser(Bzl)-OH, Boc-Phe-OH, Boc-Aib-OH, Boc-Glu(OcHex)-OH and Boc-Trp(Fm)-OH. The

synthesis was carried out on a 0.20 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times 5 were 5 min. except for the Boc-Aib-OH residues and the following residues, Boc-Lys(2ClZ)-OH and Boc-His(DNP)-OH wherein the coupling times were 2 hours.

At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min. to remove the DNP group on the His side chain. The N-terminal Boc group was then removed by 10 treatment with 100% TFA for 2 x 2 min. After neutralization of the peptide-resin with 10% DIEA in DMF (1 x 1 min), the formyl group on the side chain of Trp was removed by treatment with a solution of 15% ethanolamine/ 15% water/ 70% DMF for 2 x 30 min. The peptide-resin was washed with DMF and DCM and dried under reduced pressure. The final cleavage was done by stirring the peptide-resin in 15 10 mL of HF containing 1 mL of anisole and dithiothreitol (24 mg) at 0°C for 75 min. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc (6 x 10 mL).

The peptide mixture in the aqueous extract was purified on reverse-phase preparative high pressure liquid chromatography (HPLC) using a reverse phase 20 VYDAC® C₁₈ column (Nest Group, Southborough, MA). The column was eluted with a linear gradient (20% to 50% of solution B over 105 min.) at a flow rate of 10 mL/min (Solution A = water containing 0.1% TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 25 135 mg of a white solid was obtained. Purity was 98.6% based on analytical HPLC analysis. Electro-spray mass spectrometer (MS(ES))S analysis gave the molecular weight at 3339.7 (in agreement with the calculated molecular weight of 3339.7).

Example 2



30 The title compound (HEPES is (4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid)) can be synthesized as follows: after assembly of the peptide (Aib^{8,35})hGLP-1(7-36)NH₂ on MBHA resin (0.20 mmol) according to the procedure of Example 1, the peptide-resin is treated with 100% TFA (2 x 2 min.) and washed with DMF and DCM. The resin is then neutralized with 10% DIEA in DMF for 2 min.

After washing with DMF and DCM, the resin is treated with 0.23 mmol of 2-chloro-1-ethanesulfonyl chloride and 0.7 mmol of DIEA in DMF for about 1 hour. The resin is washed with DMF and DCM and treated with 1.2 mmol of 2-hydroxyethylpiperazine for about 2 hours. The resin is washed with DMF and DCM 5 and treated with different reagents ((1) 20% mercaptoethanol / 10% DIEA in DMF and (2) 15% ethanolamine / 15% water / 70% DMF) to remove the DNP group on the His side chain and formyl group on the Trp side chain as described above before the final HF cleavage of the peptide from the resin.

Example 3

10 $((N_{\alpha}\text{-HEPA-His})^7, \text{Aib}^{8,35})\text{hGLP-1(7-36)NH}_2$

The title compound (HEPA is (4-(2-hydroxyethyl)-1-piperazineacetyl)) can be made substantially according to the procedure described in Example 2 for making $((N_{\alpha}\text{-HEPES-His})^7, \text{Aib}^{8,35})\text{hGLP-1(7-36)NH}_2$ except that 2-bromoacetic anhydride is used in place of 2-chloro-1-ethanesulfonyl chloride.

15 Example 4

$(\text{Aib}^8, \beta\text{-Ala}^{35})\text{hGLP-1(7-36)NH}_2$

The title compound was synthesized substantially according to the procedure described for Example 1 using the appropriate protected amino acids. MS (ES) gave the molecular weight at 3325.7, calculated MW = 3325.8, purity = 20 99%, yield = 85 mg.

The synthesis of other compounds of the present invention can be accomplished in substantially the same manner as the procedure described for the synthesis of $(\text{Aib}^{8,35})\text{hGLP-1(7-36)NH}_2$ in Example 1 above, but using the appropriate protected amino acids depending on the desired peptide.

25 Example 5

$(\text{Aib}^{8,35}, \text{Arg}^{26,34}, \text{Lys}^{36}(\text{N}_\epsilon\text{-tetradecanoyl}))\text{hGLP-1(7-36)NH}_2$

The Boc amino acids used were the same as those in the synthesis of $(\text{Aib}^{8,35})\text{hGLP-1(7-36)NH}_2$ described in Example 1 except that Fmoc-Lys(Boc)-OH was used in this example. The first amino acid residue was coupled to the resin 30 manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH was dissolved in 4 mL of 0.5N HBTU in DMF. To the solution was added 1 mL of DIEA. The mixture was shaken for about 2 min. To the solution was then added 0.2 mmol of MBHA resin (substitution = 0.91 mmol/g). The mixture was shaken for about 1 hr. The resin was washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc

protecting group. The resin was washed with DMF. Myristic acid (2.5 mmol) was pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF for 2 min and was coupled to the Fmoc-Lys-resin. The coupling time was about 1 hr. The resin was washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin was washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The following steps synthesis and purification procedures for the peptide were the same as those in the synthesis of (Aib^{8,35})hGLP-1(7-36)NH₂ in Example 1. 43.1 mg of the title compound were obtained as a white solid. Purity was 98% based on analytical HPLC analysis.

10 Electro-spray mass spectrometer analysis gave the molecular weight at 3577.7 in agreement with the calculated molecular weight 3578.7.

Examples 6-8

Examples 6-8 were synthesized substantially according to the procedure described for Example 5 using the appropriate protected amino acid and the appropriate acid in place of the Myristic acid used in Example 5.

15 Example 6: (Aib^{8,35}, Arg²⁸, Lys³⁴(N_ε-tetradecanoyl))hGLP-1(7-36)NH₂; Yield = 89.6 mg; MS(ES) = 3577.2; Calculated MW = 3578.7; Purity 96%.

Example 7: (Aib^{8,35,37}, Arg^{28,34}, Lys³⁸(N_ε-tetradecanoyl))hGLP-1(7-38)NH₂; Yield = 63.3 mg; MS(ES) = 3818.7; Calculated MW = 3819.5; Purity 96%.

20 Example 8: (Aib^{8,35}, Arg^{28,34}, Lys³⁶(N_ε-decanoic acid))hGLP-1(7-36)NH₂; Yield = 57.4 mg; MS(ES) = 3521.5; Calculated MW = 3522.7; Purity 98%; Acid = decanoic acid.

25 The syntheses of other compounds of the present invention containing Lys(N_ε-alkanoyl) residue can be carried out in an analogous manner to the procedure described for Example 5, (Aib^{8,35}, Arg^{28,34}, Lys³⁶(N_ε-tetradecanoyl))hGLP-1(7-36)NH₂. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N_ε-alkanoyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. If the Lys(N_ε-alkanoyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N_ε-alkanoyl) residue is assembled on the resin on the peptide synthesizer first. The appropriate acid corresponding to the desired alkanoyl can be purchased from Aldrich Chemical Co., Inc. Milwaukee, WI, USA, e.g., octanoic acid, decanoic acid, lauric acid and palmitic acid.

Example 9

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N-dodecanesulfonyl))hGLP-1(7-36)NH₂

The Boc amino acids to be used in this synthesis are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA resin(substitution = 0.91 mmol/g). The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF and to it is added 0.25 mmol of 1-dodecanesulfonyl chloride in 4 mL of DMF and 1 mL of DIEA. The mixture is shaken for about 2 hrs. The resin is washed with DMF and treated with 25% piperidine in DMF for 2 x 20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer. The synthesis of the rest of the peptide and purification procedures are the same as those described in Example 1.

The syntheses of other compounds of the present invention containing Lys(N-alkylsulfonyl) residue can be carried out in an analogous manner to the procedure described in Example 9. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N-alkylsulfonyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. If the Lys(N-alkylsulfonyl) residue is not at the C-terminus, the peptide fragment immediately prior to the Lys(N-alkylsulfonyl) residue is assembled on the resin on the peptide synthesizer first. The appropriate alkylsulfonyl chloride can be obtained from Lancaster Synthesis Inc., Windham, NH, USA, e.g., 1-octanesulfonyl chloride, 1-decanesulfonyl chloride, 1-dodecanesulfonyl chloride, 1-hexadecanesulfonyl chloride and 1-octadecylsulfonyl chloride.

Example 10

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

The Boc amino acids to be used for this example are the same as those used in the synthesis of Example 5. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Lys(Boc)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution =

0.91 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x2 min to remove the Boc protecting group. The resin is washed with DMF. The 2-bromoacetic acid (2.5 mmol) is pre-activated with HBTU (2.0 mmol) and DIEA (1 mL) in 4 mL of DMF for about 2 min and is 5 added to the resin. The mixture is shaken for about 10 min and washed with DMF. The resin is then treated with 1.2 mmol of piperazine in 4 mL of DMF for about 2 hrs. The resin is washed with DMF and treated with 2 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic 10 anhydride and 1 mL of DIEA in 4 mL of DMF for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min. The resin is washed 15 with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The remaining synthesis and purification procedures for the peptide are the same as the procedures described for Example 1.

The syntheses of other compounds of the present invention containing 15 Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 10. Fmoc-Lys(Boc)-OH amino acid is used for the residue of Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys. The corresponding iodoalkane is used for the residue of Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue is not at the C-terminus, the peptide fragment 20 immediately prior to the Lys(N_ε-(2-(4-alkyl-1-piperazine)-acetyl)) residue is assembled on the resin on the peptide synthesizer first.

Example 11

25 (Aib^{8,35}, Arg^{28,34}, Asp³⁶(1-(4-tetradecyl-piperazine)))hGLP-1(7-36)NH₂

The Boc amino acids to be used in this example are the same as the amino acids used in synthesis of Example 5 except Fmoc-Asp(O-tBu)-OH is used at position 36. The first amino acid residue is coupled to the resin manually on a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N HBTU in 30 DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.91 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the tBu protecting group. The resin is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL

of DMF for about 15 min. 0.6 mmol of piperazine is added to the reaction mixture and the mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 3 mmol of 1-iodotetradecane for about 4 hrs. After washing with DMF, the resin is treated with 3 mmol of acetic anhydride and 1 mL of DIEA in 4 mL of DMF 5 for about 0.5 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction vessel of the peptide synthesizer to continue the synthesis. The remaining synthesis and purification procedures for the peptide are the same as those for the synthesis of Example 1.

10 The syntheses of other compounds of the present invention comprising Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue are carried out in an analogous manner as the procedure described for the synthesis of Example 11. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) in the peptide, while Boc- 15 Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu. The corresponding iodoalkane is used for the residue of Lys(N-(2-(4-alkyl-1-piperazine)-acetyl)) during the alkylation step. If the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-(4-alkylpiperazine)) or Glu(1-(4-alkylpiperazine)) 20 residue is assembled on the resin on the peptide synthesizer first.

Example 12

(Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-tetradecylamino))hGLP-1(7-36)NH₂

The Boc amino acids to be used for this example are the same as those used in Example 5. The first amino acid residue is coupled to the resin manually on 25 a shaker. 2.5 mmol of Fmoc-Asp(O-tBu)-OH is dissolved in 4 mL of 0.5N HBTU in DMF. To the solution is added 1 mL of DIEA. The mixture is shaken for about 2 min. To the solution is then added 0.2 mmol of MBHA (substitution = 0.91 mmol/g) resin. The mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 100% TFA for 2x15 min to remove the t-Bu protecting group. The resin 30 is washed with DMF and is treated with HBTU (0.6 mmol) and DIEA (1mL) in 4 mL of DMF for about 15 min. 0.6 mmol of 1-tetradecaneamine is added to the reaction mixture and the mixture is shaken for about 1 hr. The resin is washed with DMF and treated with 25% piperidine in DMF for 2x20 min to remove the Fmoc protecting group. The resin is washed with DMF and transferred to the reaction

vessel of the peptide synthesizer to continue the synthesis. The remaining synthesis and purification procedures for the peptide of this example are the same as those described for the synthesis of Example 1.

The syntheses of other compounds of the present invention containing 5 Asp(1-alkylamino) or Glu(1-alkylamino) residue are carried out in an analogous manner as described for the synthesis of Example 12. Fmoc-Asp(O-tBu)-OH or Fmoc-Glu(O-tBu)-OH amino acid is used for the residue of Asp(1-alkylamino) or Glu(1-alkylamino), respectively, in the peptide, while Boc-Asp(OcHex)-OH or Boc-Glu(OcHex)-OH amino acid is used for the residue of Asp or Glu, respectively. If 10 the Asp(1-alkylamino) or Glu(1-alkylamino) residue is not at the C-terminus, the peptide fragment immediately prior to the Asp(1-alkylamino) or Glu(1-alkylamino) residue is assembled on the resin on the peptide synthesizer first.

Example 13

(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N-tetradecanoyl), β -Ala³⁷)hGLP-1(7-37)-OH

15 The Boc amino acids used are the same as those in the synthesis of (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N-tetradecanoyl))hGLP-1(7-36)NH₂ (Example 5). 270 mg of Boc- β -Ala-PAM resin (Novabiochem, San Diego, California, substitution=0.74 mmol/g) was used. The Boc protecting group on Boc- β -Ala-PAM resin was deblocked on a shaker with 100%TFA for 2x2 min first. The remainder of the 20 synthesis and purification procedures were the same as that in Example 5. 83.0 mg of the title peptide was obtained as white solid. Purity was 99% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 3650.5 in agreement with the calculated weight 3650.8.

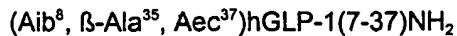
Example 14

25 (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N-tetradecanoyl))hGLP-1(7-36)-OH

The Boc amino acids to be used are the same as those in the synthesis of (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N-tetradecanoyl))hGLP-1(7-36)NH₂ (Example 5). Fmoc-Lys(Boc)-OH (2.5 mmol) is pre-activated with HBTU (2.0 mmol), HOEt (2.0 mmol and DIEA (2.5 ml) in DMF (4 ml) for about 2 min. This amino acid is coupled to 235 30 mg of PAM resin (Chem-Impex, Wood Dale, IL; substitution = 0.85 mmol/g) manually on a shaker. The coupling time is about 8 hrs. The remainder of the synthesis and purification procedures are the same as those in Example 5. Electro-spray mass spectrometer analysis gave the molecular weight at 3579.15 in agreement with the calculated weight 3579.5.

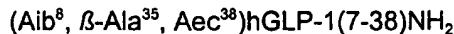
The syntheses of other analogs of hGLP-1(7-36)-OH, hGLP-1(7-37)-OH and hGLP-1(7-38)-OH of the instant invention which contain Lys(N_ε-alkanoyl) residue can be carried out in an analogous manner according to the procedure described for the synthesis of Example 14. Fmoc-Lys(Boc)-OH amino acid is used 5 for the residue of Lys(N_ε-alkanoyl) in the peptide, while Boc-Lys(2ClZ)-OH amino acid is used for the residue of Lys.

Example 366



A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Fmoc-Aec-10 OH (0.40g, 0.829 mmol), HBTU (1.5 mL @ 0.5M in DMF) and DIEA (0.5mL) in a reaction vessel was shaken on a shaker for 4h at room temperature. The resin was then washed with DMF and treated with 25% piperidine in DMF for 2X20min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according 15 to the procedure described for Example 1. The purification procedure was also the same as the one described in Example 1. Electro-spray mass spectrometer analysis gave the molecular weight at 3494.8 in agreement with the calculated molecular weight 3494.99. Purity 93%; Yield 79.1mg.

20 Example 367



Example 367 was synthesized substantially according to the procedure described for Example 366. MS(ES)=3551.7, calculated MW=3552.04; Purity 97%; Yield 97.4mg.

25 Example 368:



A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Fmoc-Aec-30 OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL) in a reaction vessel was shaken on a shaker for 2h at room temperature. The resin was then washed with DMF and treated with 30% piperidine in DMF for 2X15min. The resin was washed with DMF. To the reaction vessel were added Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL). The mixture was shaken at room temperature for 2h. The resin was washed with DMF

and treated with 30% piperidine in DMF for 2X15min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described 5 in Example 1. Electro-spray mass spectrometer analysis gave the molecular weight at 3663.9 in agreement with the calculated molecular weight 3664.26. Purity 100%; Yield 75.3mg.

Example 369

10 (Aib⁸, Arg^{28,34}, β -Ala³⁵, Lys³⁶(N^c-Aec-decanoyl))hGLP-1(7-36)NH₂
A mixture of MBHA resin (0.2mmol, substitution=0.91mmol/g), Boc-Lys(Fmoc)-OH (1.17g, 2.5mmol), HBTU (4 mL @ 0.5M in DMF) and DIEA (1mL) in a reaction vessel was shaken on a shaker at room temperature for 10min. The resin was washed with DMF and treated with 25% piperidine in DMF for 2X15min.
15 The resin was washed with DMF. To the reaction vessel were added Fmoc-Aec-OH (0.289g, 0.6 mmol), HBTU (1.12 mL @ 0.5M in DMF) and DIEA (0.4mL). The mixture was shaken at room temperature for 10min. The resin was washed with DMF and treated with 30% piperidine in DMF for 2X15min. The resin was washed with DMF and treated with a mixture of decanoic acid (431mg, 2.5 mmol), HBTU (4
20 mL @ 0.5M in DMF) and DIEA (1mL) for 10 min. The resin was washed with DMF and treated with 100% TFA for 2X2 min. The resin was washed with DMF and DCM and transferred to the reaction vessel of the peptide synthesizer to continue the assembly of the rest of the peptide according the procedure described for Example 1. The purification procedure was also the same as the one described in
25 Example 1. Electro-spray mass spectrometer analysis gave the molecular weight at 3677.0 in agreement with the calculated molecular weight 3677.25. Purity 97.6%;Yield 44.8mg.

The following examples can be made according to the appropriate procedures described hereinabove.

30 Example 15: (Aib³⁵)hGLP-1(7-36)NH₂

Example 16: (β -Ala³⁵)hGLP-1(7-36)NH₂

Example 17: ((N^c-Me-His)⁷, Aib^{8,35})hGLP-1(7-36)NH₂

Example 18: ((N^c-Me-His)⁷, Aib⁸, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 19: ((N^c-Me-His)⁷, Aib^{8,35}, Arg^{28,34})hGLP-1(7-36)NH₂

Example 20: ((N^a-Me-His)⁷, Aib⁸, Arg^{26,34}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 21: (Aib⁸, A6c³⁵)hGLP-1(7-36)NH₂

Example 22: (Aib⁸, A5c³⁵)hGLP-1(7-36)NH₂

Example 23: (Aib⁸, D-Ala³⁵)hGLP-1(7-36)NH₂

5 Example 24: (Aib^{8,35}, A6c³²)hGLP-1(7-36)NH₂

Example 25: (Aib^{8,35}, A5c³²)hGLP-1(7-36)NH₂

Example 26: (Aib^{8,35}, Glu²³)hGLP-1(7-36)NH₂

Example 27: (Aib^{8,24,35})hGLP-1(7-36)NH₂

Example 28: (Aib^{8,30,35})hGLP-1(7-36)NH₂

10 Example 29: (Aib^{8,25,35})hGLP-1(7-36)NH₂

Example 30: (Aib^{8,35}, A6c^{16,20})hGLP-1(7-36)NH₂

Example 31: (Aib^{8,35}, A6c^{16,29,32})hGLP-1(7-36)NH₂

Example 32: (Aib^{8,35}, A6c^{20,32})hGLP-1(7-36)NH₂

Example 33: (Aib^{8,35}, A6c²⁰)hGLP-1(7-36)NH₂

15 Example 34: (Aib^{8,35}, Lys²⁵)hGLP-1(7-36)NH₂

Example 35: (Aib^{8,24,35}, A6c²⁰)hGLP-1(7-36)NH₂

Example 36: (Aib^{8,35}, A6c^{29,32})hGLP-1(7-36)NH₂

Example 37: (Aib^{8,24,35}, A6c^{29,32})hGLP-1(7-36)NH₂

Example 38: (Aib^{8,35}, A6c¹²)hGLP-1(7-36)NH₂

20 Example 39: (Aib^{8,35}, Cha²⁰)hGLP-1(7-36)NH₂

Example 40: (Aib^{8,35}, A6c³³)hGLP-1(7-36)NH₂

Example 41: (Aib^{8,35}, A6c^{20,32})hGLP-1(7-36)NH₂

Example 42: (Aib⁸, A6c^{16,20}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 43: (Aib^{8,35}, β -Ala²²)hGLP-1(7-36)NH₂

25 Example 44: (Aib^{8,22,35})hGLP-1(7-36)NH₂

Example 45: (Aib^{8,35}, Glu²³, A6c³²)hGLP-1(7-36)NH₂

Example 46: (Aib^{8,24,35}, Glu²³, A6c³²)hGLP-1(7-36)NH₂

Example 47: (Aib^{8,24,25,35}, Glu²³, A6c³²)hGLP-1(7-36)NH₂

Example 48: (Aib^{8,24,25,35}, A6c^{16,20,32}, Glu²³)hGLP-1(7-36)NH₂

30 Example 49: (Aib⁸, A6c³², β -Ala³⁵)hGLP-1(7-36)NH₂

Example 50: (Aib⁸, A5c³², β -Ala³⁵)hGLP-1(7-36)NH₂

Example 51: (Aib⁸, Glu²³, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 52: (Aib^{8,24}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 53: (Aib^{8,30}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 54: (Aib^{8,25}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 55: (Aib⁸, A6c^{16,20}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 56: (Aib⁸, A6c^{16,29,32}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 57: (Aib⁸, A6c^{20,32}, β -Ala³⁵)hGLP-1(7-36)NH₂

5 Example 58: (Aib⁸, A6c²⁰, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 59: (Aib⁸, Lys²⁵, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 60: (Aib^{8,24}, A6c²⁰, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 61: (Aib⁸, A6c^{29,32}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 62: (Aib^{8,24}, A6c^{29,32}, β -Ala³⁵)hGLP-1(7-36)NH₂

10 Example 63: (Aib⁸, A6c¹², β -Ala³⁵)hGLP-1(7-36)NH₂

Example 64: (Aib⁸, Cha²⁰, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 65: (Aib⁸, A6c³³, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 66: (Aib⁸, A6c^{20,32}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 67: (Aib⁸, β -Ala^{22,35})hGLP-1(7-36)NH₂

15 Example 68: (Aib^{8,22}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 69: (Aib⁸, Glu²³, A6c³², β -Ala³⁵)hGLP-1(7-36)NH₂

Example 70: (Aib^{8,24}, Glu²³, A6c³², β -Ala³⁵)hGLP-1(7-36)NH₂

Example 71: (Aib^{8,24}, Glu²³, A6c³², Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 72: (Aib^{8,24,25}, Glu²³, A6c³², β -Ala³⁵)hGLP-1(7-36)NH₂

20 Example 73: (Aib^{8,24,25}, A6c^{16,20,32}, Glu²³, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 74: (Aib^{8,35}, D-Arg³⁶)hGLP-1(7-36)NH₂

Example 75: (Aib^{8,35}, D-Lys³⁶)hGLP-1(7-36)NH₂

Example 76: (Aib⁸, β -Ala³⁵, D-Arg³⁶)hGLP-1(7-36)NH₂

Example 77: (Aib⁸, β -Ala³⁵, D-Lys³⁶)hGLP-1(7-36)NH₂

25 Example 78: (Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH₂

Example 79: (Aib⁸, Arg^{26,34}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 80: (Aib^{8,35}, Arg^{25,26,34})hGLP-1(7-36)NH₂

Example 81: (Aib⁸, Arg^{25,26,34}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 82: (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)OH

30 Example 83: (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-37)OH

Example 84: (Aib^{8,35,37}, Arg^{26,34}, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-37)OH

Example 85: (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-tetradecanoyl), D-Ala³⁷)hGLP-1(7-37)OH

Example 86: (Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^c-tetradecanoyl))hGLP-1(7-38)OH

Example 87: (Aib^{8,35}, Arg^{26,34}, β -Ala³⁷, Lys³⁸(N^c-tetradecanoyl))hGLP-1(7-38)OH

Example 88: (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-38)OH

Example 89: (Aib⁸, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), β-Ala³⁷)hGLP-1(7-37)OH

Example 90: (Aib^{8,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-37)OH

Example 91: (Aib^{8,35}, Arg^{26,34}, Ado³⁷)hGLP-1(7-37)OH

5 Example 92: (Aib^{8,35}, Arg^{26,34}, Ado³⁷)hGLP-1(7-37)NH₂

Example 93: (Aib⁸, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl), D-Ala³⁷)hGLP-1(7-37)OH

Example 94: (Aib^{8,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-38)OH

Example 95: (Aib⁸, Arg^{26,34}, β-Ala³⁷, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-38)OH

Example 96: (Aib^{8,35}, Lys²⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

10 Example 97: (Aib^{8,35}, Lys²⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 98: (Aib^{8,35}, Lys²⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 99: (Aib⁸, Lys²⁶(N^ε-octanoyl), β-Ala³⁵)hGLP-1(7-36)NH₂

Example 100: (Aib⁸, Lys²⁶(N^ε-tetradecanoyl), β-Ala³⁵)hGLP-1(7-36)NH₂

Example 101: (Aib⁸, Lys²⁶(N^ε-hexadecanoyl), β-Ala³⁵)hGLP-1(7-36)NH₂

15 Example 102: (Aib^{8,35}, Lys²⁶(N^ε-octanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 103: (Aib^{8,35}, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 104: (Aib^{8,35}, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 105: (Aib^{8,35}, Lys²⁶(N^ε-decanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 106: (Aib^{8,35}, Lys²⁵, Lys²⁶(N^ε-octanoyl), Arg³⁴)hGLP-1(7-36)NH₂

20 Example 107: (Aib^{8,35}, Lys²⁵, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 108: (Aib^{8,35}, Lys²⁵, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 109: (Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 110: (Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 111: (Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

25 Example 112: (Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-decanoyl))hGLP-1(7-36)NH₂

Example 113: (Aib⁸, Lys²⁶(N^ε-octanoyl), Arg³⁴, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 114: (Aib⁸, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 115: (Aib⁸, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 116: (Aib⁸, Lys²⁶(N^ε-decanoyl), Arg³⁴, β-Ala³⁵)hGLP-1(7-36)NH₂

30 Example 117: (Aib^{8,35}, Lys³⁴(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 118: (Aib^{8,35}, Lys³⁴(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 119: (Aib^{8,35}, Lys³⁴(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 120: (Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 121: (Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 122: (Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-decanoyl))hGLP-1(7-36)NH₂

Example 123: (Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-octanoyl))hGLP-1(7-36)NH₂

5 Example 124: (Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 125: (Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 126: (Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-decanoyl))hGLP-1(7-36)NH₂

Example 127: (Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 128: (Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

10 Example 129: (Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 130: (Aib^{8,35}, Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 131: (Aib^{8,35}, Lys³⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 132: (Aib^{8,35}, Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 133: (Aib^{8,35}, Arg²⁶, Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

15 Example 134: (Aib^{8,35}, Arg²⁶, Lys³⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 135: (Aib^{8,35}, Arg²⁶, Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 136: (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 137: (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 138: (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-octanoyl))hGLP-1(7-38)NH₂

20 Example 139: (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-decanoyl))hGLP-1(7-38)NH₂

Example 140: (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-38)NH₂

Example 141: (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-hexadecanoyl))hGLP-1(7-38)NH₂

Example 142: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-octanoyl))hGLP-1(7-38)NH₂

Example 143: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-decanoyl))hGLP-1(7-38)NH₂

25 Example 144: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-38)NH₂

Example 145: (Aib^{8,35,37}, Arg^{25,28,34}, Lys³⁸(N^ε-hexadecanoyl))hGLP-1(7-38)NH₂

Example 146: (Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-octanoyl))hGLP-1(7-38)NH₂

Example 147: (Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-decanoyl))hGLP-1(7-38)NH₂

Example 148: (Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-hexadecanoyl))hGLP-1(7-38)NH₂

30 Example 149: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-octanoyl))hGLP-1(7-38)NH₂

Example 150: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-decanoyl))hGLP-1(7-38)NH₂

Example 151: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-38)NH₂

Example 152: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^c-hexadecanoyl))hGLP-1(7-38)NH₂

Example 153: (Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁸(N^c-octanoyl))hGLP-1(7-36)NH₂

Example 154: (Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁸(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

Example 155: (Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁸(N^c-hexadecanoyl))hGLP-1(7-36)NH₂

5 Example 156: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^c-octanoyl))hGLP-1(7-36)NH₂

Example 157: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

Example 158: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^c-hexadecanoyl))hGLP-1(7-36)NH₂

Example 159: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^c-decanoyl))hGLP-1(7-36)NH₂

Example 160: (Aib⁸, Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

10 Example 161: (Aib⁸, Lys³⁴(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 162: (Aib⁸, Lys³⁴(N^c-hexadecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 163: (Aib⁸, A6c³², Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 164: (Aib⁸, Glu²³, Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 165: (Aib⁸, Glu²³, A6c³², Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

15 Example 166: (Aib⁸, Arg²⁶, Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 167: (Aib⁸, Arg²⁶, Lys³⁴(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 168: (Aib⁸, Arg²⁶, Lys³⁴(N^c-hexadecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 169: (Aib⁸, Arg²⁶, Lys³⁴(N^c-decanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 170: (Aib⁸, Arg^{25,26}, Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

20 Example 171: (Aib⁸, Arg^{25,26}, Lys³⁴(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 172: (Aib⁸, Arg^{25,26}, Lys³⁴(N^c-hexadecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 173: (Aib⁸, Arg^{25,26}, Lys³⁴(N^c-decanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 174: (Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 175: (Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

25 Example 176: (Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^c-hexadecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 177: (Aib⁸, β -Ala³⁵, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂

Example 178: (Aib⁸, β -Ala³⁵, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

Example 179: (Aib⁸, β -Ala³⁵, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂

Example 180: (Aib⁸, Arg²⁶, β -Ala³⁵, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂

30 Example 181: (Aib⁸, Arg²⁶, β -Ala³⁵, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

Example 182: (Aib⁸, Arg²⁶, β -Ala³⁵, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂

Example 183: (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂

Example 184: (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

Example 185: (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c- hexadecanoyl))hGLP-1(7-36)NH₂

Example 186: (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-decanoyl))hGLP-1(7-36)NH₂

Example 187: (Aib⁸, Lys²⁵, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂

5 **Example 188:** (Aib⁸, Lys²⁵, Arg^{26,34}, Lys³⁶(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂

Example 189: (Aib⁸, Lys²⁵, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂

Example 190: (Aib⁸, Arg^{25,26,34}, β -Ala³⁵, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂

Example 191: (Aib⁸, Arg^{25,26,34}, β -Ala³⁵, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

10 **Example 192:** (Aib⁸, Arg^{25,26,34}, β -Ala³⁵, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂

Example 193: (Aib⁸, Arg^{25,26,34}, β -Ala³⁵, Lys³⁶(N^c-decanoyl))hGLP-1(7-36)NH₂

Example 194: (Aib^{8,35}, Lys²⁶(N^c-octanoyl), A6c³², Arg³⁴)hGLP-1(7-36)NH₂

Example 195: (Aib^{8,35}, Lys²⁶(N^c-tetradecanoyl), A6c³², Arg³⁴)hGLP-1(7-36)NH₂

Example 196: (Aib^{8,35}, Lys²⁶(N^c-hexadecanoyl), A6c³², Arg³⁴)hGLP-1(7-36)NH₂

15 **Example 197:** (Aib^{8,35}, A6c³², Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂

Example 198: (Aib^{8,35}, A6c³², Lys³⁴(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

Example 199: (Aib^{8,35}, A6c³², Lys³⁴(N^c-hexadecanoyl))hGLP-1(7-36)NH₂

Example 200: (Aib^{8,35}, Arg²⁶, A6c³², Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂

Example 201: (Aib^{8,35}, Arg²⁶, A6c³², Lys³⁴(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

20 **Example 202:** (Aib^{8,35}, A6c³², Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂

Example 203: (Aib^{8,35}, A6c³², Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

Example 204: (Aib^{8,35}, A6c³², Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂

Example 205: (Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂

Example 206: (Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

25 **Example 207:** (Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂

Example 208: (Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂

Example 209: (Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^c-decanoyl))hGLP-1(7-36)NH₂

Example 210: (Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂

Example 211: (Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂

30 **Example 212:** (Aib^{8,24,35}, Lys²⁶(N^c-octanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 213: (Aib^{8,24,35}, Lys²⁶(N^c-tetradecanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 214: (Aib^{8,24,35}, Lys²⁶(N^c-hexadecanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 215: (Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 216: (Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 217: (Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 218: (Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

5 Example 219: (Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 220: (Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 221: (Aib^{8,24,35}, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 222: (Aib^{8,35}, Glu²³, Lys²⁶(N^ε-octanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 223: (Aib^{8,35}, Glu²³, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴)hGLP-1(7-36)NH₂

10 Example 224: (Aib^{8,35}, Glu²³, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 225: (Aib^{8,35}, Glu²³, Lys³⁴(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 226: (Aib^{8,35}, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 227: (Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 228: (Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

15 Example 229: (Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 230: (Aib^{8,35}, Glu²³, Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 231: (Aib^{8,35}, Glu²³, Lys³⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 232: (Aib^{8,35}, Glu²³, Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 233: (Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

20 Example 234: (Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 235: (Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 236: (Aib^{8,30,35}, Lys²⁶(N^ε-octanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 237: (Aib^{8,30,35}, Lys²⁶(N^ε-tetradecanoyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 238: (Aib^{8,30,35}, Lys²⁶(N^ε-hexadecanoyl), Arg³⁴)hGLP-1(7-36)NH₂

25 Example 239: (Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 240: (Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 241: (Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 242: (Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 243: (Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

30 Example 244: (Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 245: (Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 246: (Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 247: (Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

Example 248: (Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 249: (Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 250: (Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

5 Example 251: (Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 252: (Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 253: (Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

10 Example 254: (Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-octanoyl))hGLP-1(7-36)NH₂

Example 255: (Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂

Example 256: (Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂

15 Example 257: ((N^α-HEPES-His)⁷, Aib³⁵)hGLP-1(7-36)NH₂

Example 258: ((N^α-HEPES-His)⁷, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 259: ((N^α-HEPES-His)⁷, Aib⁸, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 260: ((N^α-HEPA-His)⁷, Aib³⁵)hGLP-1(7-36)NH₂

Example 261: ((N^α-HEPA-His)⁷, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 262: ((N^α-HEPA-His)⁷, Aib⁸, β-Ala³⁵)hGLP-1(7-36)NH₂

20 Example 263: ((N^α-tetradecanoyl-His)⁷, Aib³⁵)hGLP-1(7-36)NH₂

Example 264: ((N^α-tetradecanoyl-His)⁷, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 265: ((N^α-tetradecanoyl-His)⁷, Aib^{8,35})hGLP-1(7-36)NH₂

Example 266: ((N^α-tetradecanoyl-His)⁷, Aib⁸, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 267: ((N^α-tetradecanoyl-His)⁷, Arg^{26,34}, Aib³⁵)hGLP-1(7-36)NH₂

25 Example 268: ((N^α-tetradecanoyl-His)⁷, Arg^{26,34}, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 269: ((N^α-tetradecanoyl-His)⁷, Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH₂

Example 270: ((N^α-tetradecanoyl-His)⁷, Aib⁸, Arg^{26,34}, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 271: ((N^α-tetradecanoyl-His)⁷, Arg^{25,26,34}, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 272: ((N^α-tetradecanoyl-His)⁷, Aib^{8,35}, Arg^{25,26,34})hGLP-1(7-36)NH₂

30 Example 273: ((N^α-tetradecanoyl-His)⁷, Aib⁸, Arg^{25,26,34}, β-Ala³⁵)hGLP-1(7-36)NH₂

Example 274: (Aib^{8,35}, Lys²⁶(N^ε-octanesulfonyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 275: (Aib^{8,35}, Lys²⁶(N^ε-dodecanesulfonyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 276: (Aib^{8,35}, Lys²⁸(N^c-hexadecanesulfonyl), Arg³⁴)hGLP-1(7-36)NH₂

Example 277: (Aib^{8,35}, Arg²⁶, Lys³⁴(N^c-octanesulfonyl))hGLP-1(7-36)NH₂

Example 278: (Aib^{8,35}, Arg²⁶, Lys³⁴(N^c-dodecanesulfonyl))hGLP-1(7-36)NH₂

Example 279: (Aib^{8,35}, Arg²⁶, Lys³⁴(N^c-hexadecanesulfonyl))hGLP-1(7-36)NH₂

5 Example 280: (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-octanesulfonyl))hGLP-1(7-36)NH₂

Example 281: (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-hexadecanesulfonyl))hGLP-1(7-36)NH₂

Example 282: (Aib^{8,35}, Asp²⁸(1-(4-decylpiperazine)), Arg³⁴)hGLP-1(7-36)NH₂

Example 283: (Aib^{8,35}, Asp²⁸(1-(4-dodecylpiperazine)), Arg³⁴)hGLP-1(7-36)NH₂

Example 284: (Aib^{8,35}, Asp²⁸(1-(4-tetradecylpiperazine)), Arg³⁴)hGLP-1(7-36)NH₂

10 Example 285: (Aib^{8,35}, Asp²⁶(1-(4-hexadecylpiperazine)), Arg³⁴)hGLP-1(7-36)NH₂

Example 286: (Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-decylpiperazine)))hGLP-1(7-36)NH₂

Example 287: (Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH₂

Example 288: (Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH₂

Example 289: (Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH₂

15 Example 290: (Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-36)NH₂

Example 291: (Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH₂

Example 292: (Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH₂

Example 293: (Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-38)NH₂

Example 294: (Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH₂

20 Example 295: (Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH₂

Example 296: (Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH₂

Example 297: (Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-38)NH₂

Example 298: (Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH₂

Example 299: (Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH₂

25 Example 300: (Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH₂

Example 301: (Aib^{8,35}, Arg^{25,34}, Asp²⁸(1-(4-decylpiperazine)))hGLP-1(7-36)NH₂

Example 302: (Aib^{8,35}, Arg^{25,34}, Asp²⁸(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH₂

Example 303: (Aib^{8,35}, Arg^{25,34}, Asp²⁸(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH₂

30 Example 304: (Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH₂

Example 305: (Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-decylpiperazine)))hGLP-1(7-36)NH₂

Example 306: (Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH₂

Example 307: (Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH₂

Example 308: (Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH₂

Example 309: (Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-36)NH₂

Example 310: (Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH₂

Example 311: (Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH₂

Example 312: (Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-

5 36)NH₂

Example 313: (Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-38)NH₂

Example 314: (Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH₂

Example 315: (Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH₂

Example 316: (Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-

10 38)NH₂

Example 317: (Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-38)NH₂

Example 318: (Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH₂

Example 319: (Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH₂

15 Example 320: (Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH₂

Example 321: (Aib^{8,35}, Arg^{26,34}, Glu³⁸(1-dodecylamino))hGLP-1(7-36)NH₂

Example 322: (Aib^{8,35}, Glu²⁶(1-dodecylamino), Arg³⁴)hGLP-1(7-36)NH₂

Example 323: (Aib^{8,35}, Arg²⁶, Glu³⁴(1-dodecylamino))hGLP-1(7-36)NH₂

Example 324: (Aib^{8,35,37}, Arg^{26,34}, Glu³⁸(1-dodecylamino))hGLP-1(7-38)NH₂

20 Example 325: (Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 326: (Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 327: (Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

25 Example 328: (Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 329: (Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 330: (Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

30 Example 331: (Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 332: (Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 333: (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 334: (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

5 Example 335: (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 336: (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

10 Example 337: (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 338: (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 339: (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

15 Example 340: (Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 341: (Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

20 Example 342: (Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 343: (Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 344: (Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

25 Example 345: (Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 346: (Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

30 Example 347: Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 348: (Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 349: (Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 350: (Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

5 Example 351: (Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 352: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 353: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

10 Example 354: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

Example 355: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂

15 Example 356: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 357: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

20 Example 358: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 359: (Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 360: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

25 Example 361: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 362: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 363: (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂

Example 364: (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-decanoyl))hGLP-1(7-36)OH

Example 365: (Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-decanoyl))hGLP-1(7-36)OH

Example 370 (Aib^{8,35}, Arg^{26,34}, Ava³⁷, Ado³⁸)hGLP-1(7-38)NH₂

Example 371 (Aib^{8,35}, Arg^{26,34}, Asp³⁷, Ava³⁸, Ado³⁹)hGLP-1(7-39)NH₂

Example 372 (Aib^{8,35}, Arg^{26,34}, Aun³⁷)hGLP-1(7-37)NH₂

Example 373 (Aib^{8,17,35})hGLP-1(7-36)NH₂

Example 374 (Aib⁸, Arg^{26,34}, β -Ala³⁵, D-Asp³⁷, Ava³⁸, Aun³⁹)hGLP-1(7-39)NH₂

5 Example 375 (Gly⁸, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 376 (Ser⁸, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 377 (Aib⁸, Glu^{22,23}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 378 (Gly⁸, Aib³⁵)hGLP-1(7-36)NH₂

Example 379 (Aib⁸, Lys¹⁸, β -Ala³⁵)hGLP-1(7-36)NH₂

10 Example 380 (Aib⁸, Leu²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 381 (Aib⁸, Lys³³, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 382 (Aib⁸, Lys¹⁸, Leu²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 383 (Aib⁸, D-Arg³⁶)hGLP-1(7-36)NH₂

Example 384 (Aib⁸, β -Ala³⁵, D-Arg³⁷)hGLP-1(7-37)NH₂

15 Example 385 (Aib^{8,27}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 386 (Aib^{8,27}, β -Ala^{35,37}, Arg³⁸)hGLP-1(7-38)NH₂

Example 387 (Aib^{8,27}, β -Ala^{35,37}, Arg^{38,39})hGLP-1(7-39)NH₂

Example 388 (Aib⁸, Lys^{18,27}, β -Ala³⁵)hGLP-1(7-36)NH₂

Example 389 (Aib⁸, Lys²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂

20 Example 390 (Aib⁸, β -Ala³⁵, Arg³⁸)hGLP-1(7-38)NH₂

Example 391 (Aib⁸, Arg^{26,34}, β -Ala³⁵,)hGLP-1(7-36)NH₂

Example 392 (Aib⁸, D-Arg³⁵)hGLP-1(7-36)NH₂

Example 393 (Aib⁸, β -Ala³⁵, Arg³⁷)hGLP-1(7-37)NH₂

Example 394 (Aib⁸, Phe³¹, β -Ala³⁵)hGLP-1(7-36)NH₂

25 Example 395 (Aib^{8,35}, Phe³¹)hGLP-1(7-36)NH₂

Example 396 (Aib^{8,35}, Nal³¹)hGLP-1(7-36)NH₂

Example 397 (Aib^{8,35}, Nal^{28,31})hGLP-1(7-36)NH₂

Example 398 (Aib^{8,35}, Arg^{26,34}, Nal³¹)hGLP-1(7-36)NH₂

Example 399 (Aib^{8,35}, Arg^{26,34}, Phe³¹)hGLP-1(7-36)NH₂

30 Example 400 (Aib^{8,35}, Nal^{19,31})hGLP-1(7-36)NH₂

Example 401 (Aib^{8,35}, Nal^{12,31})hGLP-1(7-36)NH₂

Example 402 (Aib^{8,35}, Lys³⁶(N^ε-decanoyl))hGLP-1(7-36)NH₂

Example 403 (Aib^{8,35}, Arg³⁴, Lys²⁸(N^ε-decanoyl))hGLP-1(7-36)NH₂

Example 404 (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-dodecanoyl))hGLP-1(7-36)NH₂

Example 405 (Aib⁸,B-Ala³⁵,Ser³⁷(O-decanoyl))hGLP1(7-37)-NH₂

Example 406 (Aib^{8,27}, β -Ala^{35,37}, Arg³⁸, Lys³⁹(N^c-octanoyl))hGLP-1(7-39)NH₂

Example 407 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-octanoyl))hGLP-1(7-37)NH₂

Example 408 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-decanoyl))hGLP-1(7-37)NH₂

5 Example 409 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-tetradecanoyl))hGLP-1(7-37)NH₂

Example 410 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-dodecanoyl))hGLP-1(7-37)NH₂

Example 411 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-dodecanoyl))hGLP-1(8-37)NH₂

Physical data for a representative sampling of the compounds exemplified herein are given in Table 1.

10

Example Number	Mol. Wt. Expected	Mol. Wt. MS(ES)	Purity (HPLC)
24	3351.8	3352.2	88%
26	3340.17	3340.9	99%
27	3353.81	3353.9	99%
29	3353.81	3353.9	99%
45	3352.6	3352.5	97%
51	3326.74	3326.6	99%
78	3395.81	3395.5	96%
136	3494	3494	99%
364	3523.02	3523.6	99%
365	3580.13	3580.3	95%
369	3677.25	3677	97%
370	3692.28	3692.4	98%
371	3807.37	3807.3	98%
372	3579.11	3579.7	97.90%
373	3337.81	3338.5	94%
374	3779.3	3779.5	94%
375	3297.7	3297.5	99%
376	3327.7	3327.4	98%
377	3398.8	3398.7	97.50%
378	3311.6	3311	93%
379	3366.85	3366.5	97%
380	3309.8	3309.4	99%
381	3354.8	3354.5	97.70%
382	3350.9	3350.3	97.20%
383	3311.73	3310.7	92%
384	3481.95	3481.3	94.30%
385	3281.76	3281.6	98%
386	3509.02	3509.1	99.40%
387	3665.2	3665.1	99%
388	3365.91	3365	97%
389	3324.79	3324.2	95%
390	3539	3539.2	93%
391	3381.74	3381.3	97%

392	3410.89	3409.8	99%
393	3481.95	3481.1	90%
394	3286.76	3286.2	99.20%
395	3300.76	3299.4	93%
396	3350.81	3349.4	99%
397	3400.87	3400.1	99%
398	3406.84	3406.4	99%
399	3356.77	3356.6	99%
400	3384.87	3384.43	94%
401	3400.87	3401.3	99%
402	3466.03	3466.9	97.40%
403	3522.05	3522.06	93%
404	3550.11	3550.2	98%
405	3567.09		99%
406	3763.38	3763.2	95%
407	3636.15	3635.8	99%
408	3664.21	3663.3	99%
409	3720.32	3719.5	99%
410	3692.27	3691.7	99%
411	3555.13	3554.4	99%

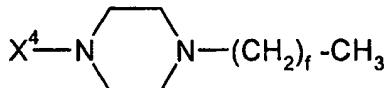
TABLE 1

CLAIMS

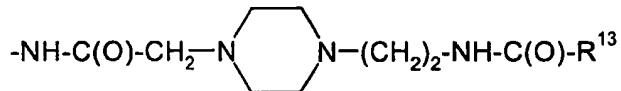
What is claimed is:

1. A compound of formula (I),
5 $(R^2R^3)-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-A^{39}-R^1$,
(I)
wherein
- A⁷ is L-His, Ura, Paa, Pta, Amp, Tma-His, des-amino-His, or deleted;
- 10 A⁸ is Ala, D-Ala, Aib, Acc, N-Me-Ala, N-Me-D-Ala or N-Me-Gly;
- A⁹ is Glu, N-Me-Glu, N-Me-Asp or Asp;
- A¹⁰ is Gly, Acc, β -Ala or Aib;
- A¹¹ is Thr or Ser;
- A¹² is Phe, Acc, Aic, Aib, 3-Pal, 4-Pal, β -Nal, Cha, Trp or X¹-Phe;
- 15 A¹³ is Thr or Ser;
- A¹⁴ is Ser or Aib;
- A¹⁵ is Asp or Glu;
- A¹⁶ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Abu, Ala or Cha;
- A¹⁷ is Ser or Thr;
- 20 A¹⁸ is Ser or Thr;
- A¹⁹ is Tyr, Cha, Phe, 3-Pal, 4-Pal, Acc, β -Nal or X¹-Phe;
- A²⁰ is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Val, Phe or X¹-Phe;
- A²¹ is Glu or Asp;
- A²² is Gly, Acc, β -Ala, Glu or Aib;
- 25 A²³ is Gln, Asp, Asn or Glu;
- A²⁴ is Ala, Aib, Val, Abu, Tle or Acc;
- A²⁵ is Ala, Aib, Val, Abu, Tle, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_n-X³)-C(O);
- A²⁶ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_n-X³)-C(O);
- 30 A²⁷ is Glu Asp, Leu, Aib or Lys;
- A²⁸ is Phe, Pal, β -Nal, X¹-Phe, Aic, Acc, Aib, Cha or Trp;
- A²⁹ is Ile, Acc, Aib, Leu, Nle, Cha, Tle, Val, Abu, Ala or Phe;
- A³⁰ is Ala, Aib or Acc;

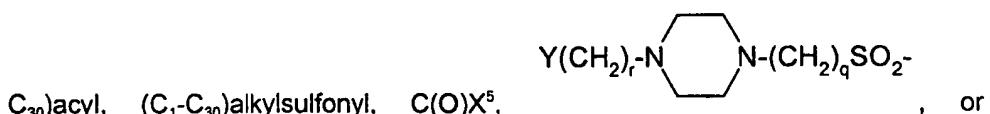
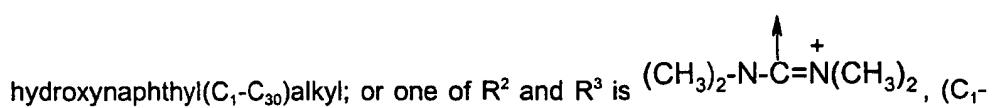
A³¹ is Trp, β -Nal, 3-Pal, 4-Pal, Phe, Acc, Aib or Cha;
 A³² is Leu, Acc, Aib, Nle, Ile, Cha, Tle, Phe, X¹-Phe or Ala;
 A³³ is Val, Acc, Aib, Leu, Ile, Tle, Nle, Cha, Ala, Phe, Abu, Lys or X¹-Phe;
 A³⁴ is Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-
 5 C(O);
 A³⁵ is Gly, β -Ala, D-Ala, Gaba, Ava, HN-(CH₂)_m-C(O), Aib, Acc or a D-amino acid;
 A³⁶ is L- or D-Arg, D- or L-Lys, D- or L-hArg, D- or L-Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), HN-CH((CH₂)_e-X³)-C(O) or deleted;
 A³⁷ is Gly, β -Ala, Gaba, Ava, Aib, Acc, Ado, Arg, Asp, Aun, Aec, HN-(CH₂)_m-C(O),
 10 HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), a D-amino acid, or deleted;
 A³⁸ is D- or L-Lys, D- or L-Arg, D- or L-hArg, D- or L-Orn, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), HN-CH((CH₂)_e-X³)-C(O) Ava, Ado, Aec or deleted;
 A³⁹ is D- or L-Lys, D- or L-Arg, HN-CH((CH₂)_n-N(R¹⁰R¹¹))-C(O), Ava, Ado, or Aec;
 X¹ for each occurrence is independently selected from the group consisting of (C₁-
 15 C₆)alkyl, OH and halo;
 R¹ is OH, NH₂, (C₁-C₃₀)alkoxy, or NH-X²-CH₂-Z⁰, wherein X² is a (C₁-
 C₁₂)hydrocarbon moiety, and Z⁰ is H, OH, CO₂H or CONH₂;

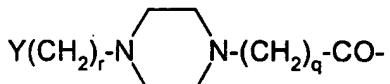


X³ is



20 or -C(O)-NHR¹², wherein X⁴ is, independently for each occurrence, -C(O)-, -NH-C(O)- or -CH₂-, and wherein f is, independently for each occurrence, an integer from 1 to 29 inclusive;
 each of R² and R³ is independently selected from the group consisting of H, (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, phenyl(C₁-C₃₀)alkyl, naphthyl(C₁-C₃₀)alkyl, hydroxy(C₁-C₃₀)alkyl, hydroxy(C₂-C₃₀)alkenyl, hydroxyphenyl(C₁-C₃₀)alkyl, and
 25 hydroxynaphthyl(C₁-C₃₀)alkyl; or one of R² and R³ is $(CH_3)_2-N-C^+=N(CH_3)_2$, (C₁-





; wherein Y is H, OH or NH₂; r is 0 to 4; q is 0 to 4;

and X^5 is $(C_1-C_{30})alkyl$, $(C_2-C_{30})alkenyl$, $phenyl(C_1-C_{30})alkyl$, $naphthyl(C_1-C_{30})alkyl$, $hydroxy(C_1-C_{30})alkyl$, $hydroxy(C_2-C_{30})alkenyl$, $hydroxyphenyl(C_1-C_{30})alkyl$ or $hydroxynaphthyl(C_1-C_{30})alkyl$;

5 e is, independently for each occurrence, an integer from 1 to 4 inclusive;
m is, independently for each occurrence, an integer from 5 to 24 inclusive;
n is, independently for each occurrence, an integer from 1 to 5, inclusive;
each of R^{10} and R^{11} is, independently for each occurrence, H, $(C_1-C_{30})alkyl$, $(C_1-C_{30})acyl$, $(C_1-C_{30})alkylsulfonyl$, $-C((NH)(NH_2))$ or



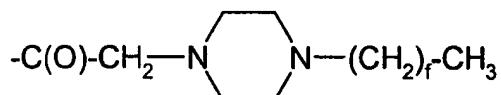
; and

R¹² and R¹³ each is, independently for each occurrence, (C₁-C₃₀)alkyl;

provided that:

when A^7 is Ura, Paa or Pta, then R^2 and R^3 are deleted;

when R^{10} is $(C_1-C_{30})\text{acyl}$, $(C_1-C_{30})\text{alkylsulfonyl}$, $-\text{C}((\text{NH})(\text{NH}_2))$ or



, then R^{11} is H or $(C_1-C_{30})\text{alkyl}$;

(i) at least one amino acid of a compound of formula (I) is not the same as the native sequence of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH;

(ii) a compound of formula (I) is not an analogue of hGLP-1(7-36, -37 or -38)NH₂ or hGLP-1(7-36, -37 or -38)OH wherein a single position has been substituted by Ala;

20 (iii) a compound of formula (I) is not (Arg^{28,34}, Lys³⁸)hGLP-1(7-38)-E, (Lys²⁸(N_c-alkanoyl))hGLP-1(7-36, -37 or -38)-E, (Lys³⁴(N_c-alkanoyl))hGLP-1(7-36, -37 or -38)-E, (Lys^{26,34}-bis(N_c-alkanoyl))hGLP-1(7-36, -37 or -38)-E, (Arg²⁶, Lys³⁴(N_c-alkanoyl))hGLP-1(8-36, -37 or -38)-E, (Arg^{28,34}, Lys³⁶(N_c-alkanoyl))hGLP-1(7-36, -37 or -38)-E or (Arg^{28,34}, Lys³⁸(N_c-alkanoyl))hGLP-1(7-38)-E, wherein E is -OH or -NH₂;

25 (iv) a compound of formula (I) is not Z¹-hGLP-1(7-36, -37 or -38)-OH, Z¹-hGLP-1(7-36, -37 or -38)-NH₂, wherein Z¹ is selected from the group consisting of:

(e) (Arg²⁵), (Arg³⁴), (Arg^{26,34}), (Lys³⁶), (Arg²⁸, Lys³⁸), (Arg³⁴, Lys³⁶), (D-Lys³⁶), (Arg³⁸), (D-Arg³⁶), (Arg^{28,34}, Lys³⁸) or (Arg^{28,36}, Lys³⁴);

- (f) (Asp²¹);
- (g) at least one of (Aib⁸), (D-Ala⁸) and (Asp⁹); and
- (h) (Tyr⁷), (N-acyl-His⁷), (N-alkyl-His⁷), (N-acyl-D-His⁷) or (N-alkyl-D-His⁷);
- (v) a compound of formula (I) is not a combination of any two of the substitutions listed in groups (a) to (d); and
- 5 (vi) a compound of formula (I) is not (N-Me-Ala⁸)hGLP-1(8-36 or -37), (Glu¹⁵)hGLP-1(7-36 or -37), (Asp²¹)hGLP-1(7-36 or -37) or (Phe³¹)hGLP-1(7-36 or -37) or a pharmaceutically acceptable salt thereof.

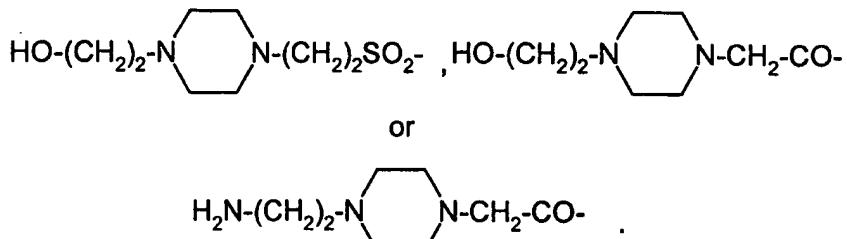
2. A compound according to claim 1, wherein A¹¹ is Thr; A¹³ is Thr; A¹⁵ 10 is Asp; A¹⁷ is Ser; A¹⁸ is Ser; A²¹ is Glu; A²³ is Gln or Glu; A²⁷ is Glu; and A³¹ is Trp; or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2, wherein A⁸ is Glu, N-Me-Glu or N-Me-Asp; A¹² is Phe, Acc or Aic; A¹⁶ is Val, Acc or Aib; A¹⁹ is Tyr; A²⁰ is Leu, Acc or Cha; A²⁴ is Ala, Aib or Acc; A²⁵ is Ala, Aib, Acc, Lys, Arg, hArg, Orn, HN-CH((CH₂)_n-15 N(R¹⁰R¹¹))-C(O) or HN-CH((CH₂)_e-X³)-C(O); A²⁸ is Phe; A²⁹ is Ile or Acc; A³⁰ is Ala or Aib; A³² is Leu, Acc or Cha; and A³³ is Val or Acc; or a pharmaceutically acceptable salt thereof.

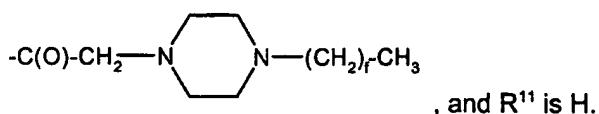
4. A compound according to claim 3, wherein A⁸ is Ala, D-Ala, Aib, A6c, A5c, N-Me-Ala, N-Me-D-Ala or N-Me-Gly; A¹⁰ is Gly; A¹² is Phe, A6c or A5c; A¹⁶ is Val, A6c or A5c; A²⁰ is Leu, A6c, A5c or Cha; A²² is Gly, β -Ala or Aib; A²⁴ is Ala or Aib; A²⁹ is Ile, A6c or A5c; A³² is Leu, A6c, A5c or Cha; A³³ is Val, A6c or A5c; A³⁵ is Aib, β -Ala, Ado, A6c, A5c or Gly; and A³⁷ is Gly, Aib, β -Ala, Ado, D-Ala or deleted; or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 4 or a pharmaceutically acceptable salt thereof, wherein X⁴ for each occurrence is -C(O)-; e for each occurrence is independently 1 or 2; and R¹ is OH or NH₂.

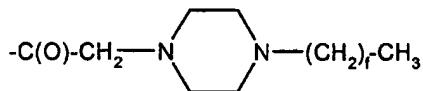
6. A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R² is H and R³ is (C₁-C₃₀)alkyl, (C₂-C₃₀)alkenyl, (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl,



7. A compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is (C₁-C₃₀)acyl, (C₁-C₃₀)alkylsulfonyl or



5 8. A compound according to claim 7 or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is (C₄-C₂₀)acyl, (C₄-C₂₀)alkylsulfonyl or



9. A compound according to claim 1 wherein said compound is (Aib^{8,35})hGLP-1(7-36)NH₂,

10 ((N_o-HEPES-His)⁷, Aib^{8,35})hGLP-1(7-36)NH₂,

((N_o-HEPA-His)⁷, Aib^{8,35})hGLP-1(7-36)NH₂,

(Aib⁸, β -Ala³⁵)hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N_c-tetradecanoyl))hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg²⁶, Lys³⁴(N_c-tetradecanoyl))hGLP-1(7-36)NH₂,

15 (Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N_c-tetradecanoyl))hGLP-1(7-38)NH₂,

(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N_c-decanoyl))hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N_c-dodecanesulfonyl))hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N_c-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-tetradecyl-piperazine)))hGLP-1(7-36)NH₂,

20 (Aib^{8,35}, Arg^{26,34}, Asp³⁶(1-tetradecylamino))hGLP-1(7-36)NH₂,

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N_c-tetradecanoyl), β -Ala³⁷)hGLP-1(7-37)-OH or

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N_c-tetradecanoyl))hGLP-1(7-36)-OH, or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 9 wherein said compound is

25 (Aib^{8,35})hGLP-1(7-36)NH₂,

(Aib⁸, β -Ala³⁵)hGLP-1(7-36)NH₂,
(Aib^{8,35}, Arg²⁶, Lys³⁴(N-tetradecanoyl))hGLP-1(7-36)NH₂,
(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N-tetradecanoyl))hGLP-1(7-38)NH₂,
(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N-decanoyl))hGLP-1(7-36)NH₂, or

5 (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N-tetradecanoyl), β -Ala³⁷)hGLP-1(7-37)-OH, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

10 12. A method of eliciting an agonist effect from a GLP-1 receptor in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

13. A method of treating a disease selected from the group consisting of 15 Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis and neurodegenerative disease, in a subject in need thereof which comprises administering to said subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

20 14. A method according to claim 13 wherein said disease is Type I diabetes or Type II diabetes.

15. A compound according to claim 1 wherein said compound is
(Aib³⁵)hGLP-1(7-36)NH₂;
(β -Ala³⁵)hGLP-1(7-36)NH₂;
25 ((N^a-Me-His)⁷, Aib^{8,35})hGLP-1(7-36)NH₂;
((N^a-Me-His)⁷, Aib⁸, β -Ala³⁵)hGLP-1(7-36)NH₂;
((N^a-Me-His)⁷, Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH₂;
((N^a-Me-His)⁷, Aib⁸, Arg^{26,34}, β -Ala³⁵)hGLP-1(7-36)NH₂;
30 (Aib⁸, A6c³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, A5c³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, D-Ala³⁵)hGLP-1(7-36)NH₂;
(Aib^{8,35}, A6c³²)hGLP-1(7-36)NH₂;
(Aib^{8,35}, A5c³²)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Glu²³)hGLP-1(7-36)NH₂;

(Aib^{8,24,35})hGLP-1(7-36)NH₂;
(Aib^{8,30,35})hGLP-1(7-36)NH₂;
(Aib^{8,25,35})hGLP-1(7-36)NH₂;
(Aib^{8,35}, A6c^{16,20})hGLP-1(7-36)NH₂;
5 (Aib^{8,35}, A6c^{16,29,32})hGLP-1(7-36)NH₂;
(Aib^{8,35}, A6c^{20,32})hGLP-1(7-36)NH₂;
(Aib^{8,35}, A6c²⁰)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys²⁵)hGLP-1(7-36)NH₂;
(Aib^{8,24,35}, A6c²⁰)hGLP-1(7-36)NH₂;
10 (Aib^{8,35}, A6c^{29,32})hGLP-1(7-36)NH₂;
(Aib^{8,24,35}, A6c^{29,32})hGLP-1(7-36)NH₂;
(Aib^{8,35}, A6c¹²)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Cha²⁰)hGLP-1(7-36)NH₂;
(Aib^{8,35}, A6c³³)hGLP-1(7-36)NH₂;
15 (Aib^{8,35}, A6c^{20,32})hGLP-1(7-36)NH₂;
(Aib⁸, A6c^{16,20}, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib^{8,35}, β -Ala²²)hGLP-1(7-36)NH₂;
(Aib^{8,22,35})hGLP-1(7-36)NH₂;
(Aib^{8,35}, Glu²³, A6c³²)hGLP-1(7-36)NH₂;
20 (Aib^{8,24,35}, Glu²³, A6c³²)hGLP-1(7-36)NH₂;
(Aib^{8,24,25,35}, Glu²³, A6c³²)hGLP-1(7-36)NH₂;
(Aib^{8,24,25,35}, A6c^{16,20,32}, Glu²³)hGLP-1(7-36)NH₂;
(Aib⁸, A6c³², β -Ala³⁵)hGLP-1(7-36)NH₂;
25 (Aib⁸, A5c³², β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, Glu²³, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib^{8,24}, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib^{8,30}, β -Ala³⁵)hGLP-1(7-36)NH₂;
30 (Aib^{8,25}, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, A6c^{16,20}, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, A6c^{20,32}, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, A6c²⁰, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, Lys²⁵, β -Ala³⁵)hGLP-1(7-36)NH₂;
35 (Aib^{8,24}, A6c²⁰, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, A6c^{29,32}, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib^{8,24}, A6c^{29,32}, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, A6c¹², β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Cha²⁰, β -Ala³⁵)hGLP-1(7-36)NH₂;

5 (Aib⁸, A6c³³, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, A6c^{20,32}, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, β -Ala^{22,35})hGLP-1(7-36)NH₂;

(Aib^{8,22}, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Glu²³, A6c³², β -Ala³⁵)hGLP-1(7-36)NH₂;

10 (Aib^{8,24}, Glu²³, A6c³², β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib^{8,24}, Glu²³, A6c³², Lys³⁴(N^ε-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib^{8,24,25}, Glu²³, A6c³², β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib^{8,24,25}, A6c^{18,20,32}, Glu²³, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib^{8,35}, D-Arg³⁶)hGLP-1(7-36)NH₂;

15 (Aib^{8,35}, D-Lys³⁶)hGLP-1(7-36)NH₂;

(Aib⁸, β -Ala³⁵, D-Arg³⁶)hGLP-1(7-36)NH₂;

(Aib⁸, β -Ala³⁵, D-Lys³⁶)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH₂;

(Aib⁸, Arg^{26,34}, β -Ala³⁵)hGLP-1(7-36)NH₂;

20 (Aib^{8,35}, Arg^{25,26,34})hGLP-1(7-36)NH₂;

(Aib⁸, Arg^{25,26,34}, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-36)OH;

(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-37)OH;

(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-37)OH;

25 (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl), D-Ala³⁷)hGLP-1(7-37)OH;

(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-38)OH;

(Aib^{8,35}, Arg^{26,34}, β -Ala³⁷, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-38)OH;

(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-38)OH;

(Aib⁸, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl), β -Ala³⁷)hGLP-1(7-37)OH;

30 (Aib^{8,37}, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-37)OH;

(Aib^{8,35}, Arg^{26,34}, Ado³⁷)hGLP-1(7-37)OH;

(Aib^{8,35}, Arg^{26,34}, Ado³⁷)hGLP-1(7-37)NH₂;

(Aib⁸, Arg^{26,34}, Lys³⁸(N^ε-tetradecanoyl), D-Ala³⁷)hGLP-1(7-37)OH;

(Aib^{8,37}, Arg^{26,34}, Lys³⁸(N^c-tetradecanoyl))hGLP-1(7-38)OH;
(Aib⁸, Arg^{26,34}, β -Ala³⁷, Lys³⁸(N^c-tetradecanoyl))hGLP-1(7-38)OH;
(Aib^{8,35}, Lys²⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys²⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
5 (Aib^{8,35}, Lys²⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
(Aib⁸, Lys²⁶(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, Lys²⁶(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, Lys²⁶(N^c-hexadecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys²⁶(N^c-octanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
10 (Aib^{8,35}, Lys²⁶(N^c-tetradecanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys²⁶(N^c-hexadecanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys²⁶(N^c-decanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys²⁵, Lys²⁶(N^c-octanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys²⁵, Lys²⁶(N^c-tetradecanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
15 (Aib^{8,35}, Lys²⁵, Lys²⁶(N^c-hexadecanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
20 (Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^c-decanoyl))hGLP-1(7-36)NH₂;
(Aib⁸, Lys²⁶(N^c-octanoyl), Arg³⁴, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, Lys²⁶(N^c-tetradecanoyl), Arg³⁴, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, Lys²⁶(N^c-hexadecanoyl), Arg³⁴, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, Lys²⁶(N^c-decanoyl), Arg³⁴, β -Ala³⁵)hGLP-1(7-36)NH₂;
25 (Aib^{8,35}, Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys³⁴(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁶, Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁶, Lys³⁴(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁶, Lys³⁴(N^c-decanoyl))hGLP-1(7-36)NH₂;
30 (Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^c-decanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys²⁵, Arg²⁶, Lys³⁴(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

5 (Aib^{8,35}, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁶, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁶, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

10 (Aib^{8,35}, Arg²⁶, Lys³⁸(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^c-octanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^c-decanoyl))hGLP-1(7-38)NH₂;

15 (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^c-tetradecanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^c-hexadecanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^c-octanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^c-decanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^c-tetradecanoyl))hGLP-1(7-38)NH₂;

20 (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^c-hexadecanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^c-octanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^c-decanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^c-hexadecanoyl))hGLP-1(7-38)NH₂;

25 (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^c-decanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^c-tetradecanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^c-hexadecanoyl))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;

30 (Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^c-decanoyl))hGLP-1(7-36)NH₂;
 (Aib⁸, Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Lys³⁴(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 5 (Aib⁸, Lys³⁴(N^c-hexadecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, A6c³², Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Glu²³, Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Glu²³, A6c³², Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Arg²⁶, Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 10 (Aib⁸, Arg²⁶, Lys³⁴(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Arg²⁶, Lys³⁴(N^c-hexadecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Arg²⁶, Lys³⁴(N^c-decanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Arg^{25,26}, Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Arg^{25,26}, Lys³⁴(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 15 (Aib⁸, Arg^{25,26}, Lys³⁴(N^c-hexadecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Arg^{25,26}, Lys³⁴(N^c-decanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^c-octanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Lys²⁵, Arg²⁶, Lys³⁴(N^c-hexadecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 20 (Aib⁸, β -Ala³⁵, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib⁸, β -Ala³⁵, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
 (Aib⁸, β -Ala³⁵, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
 (Aib⁸, Arg²⁶, β -Ala³⁵, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib⁸, Arg²⁶, β -Ala³⁵, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
 25 (Aib⁸, Arg²⁶, β -Ala³⁵, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
 30 (Aib⁸, Lys²⁵, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib⁸, Lys²⁵, Arg^{26,34}, Lys³⁶(N^c-tetradecanoyl), β -Ala³⁵)hGLP-1(7-36)NH₂;
 (Aib⁸, Lys²⁵, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

(Aib⁸, Arg^{25,26,34}, β -Ala³⁵, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;

(Aib⁸, Arg^{25,26,34}, β -Ala³⁵, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

(Aib⁸, Arg^{25,26,34}, β -Ala³⁵, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

(Aib⁸, Arg^{25,26,34}, β -Ala³⁵, Lys³⁶(N^c-decanoyl))hGLP-1(7-36)NH₂;

5 (Aib^{8,35}, Lys²⁶(N^c-octanoyl), A6c³², Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Lys²⁶(N^c-tetradecanoyl), A6c³², Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Lys²⁶(N^c-hexadecanoyl), A6c³², Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,35}, A6c³², Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, A6c³², Lys³⁴(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

10 (Aib^{8,35}, A6c³², Lys³⁴(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg²⁶, A6c³², Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg²⁶, A6c³², Lys³⁴(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, A6c³², Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, A6c³², Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

15 (Aib^{8,35}, A6c³², Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg²⁶, A6c³², Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;

20 (Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^c-decanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{26,34}, A6c³², Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,24,35}, Lys²⁶(N^c-octanoyl), Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,24,35}, Lys²⁶(N^c-tetradecanoyl), Arg³⁴)hGLP-1(7-36)NH₂;

25 (Aib^{8,24,35}, Lys²⁶(N^c-hexadecanoyl), Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,24,35}, Arg²⁶, Lys³⁴(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;

30 (Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,24,35}, Arg^{26,34}, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,24,35}, Glu²³, A6c³², Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Glu²³, Lys²⁶(N^c-octanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Lys²⁶(N^c-tetradecanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Lys²⁶(N^c-hexadecanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;

5 (Aib^{8,35}, Glu²³, A6c³², Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Arg²⁶, Lys³⁴(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;

10 (Aib^{8,35}, Glu²³, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Arg^{26,34}, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

15 (Aib^{8,30,35}, Lys²⁶(N^c-octanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
 (Aib^{8,30,35}, Lys²⁶(N^c-tetradecanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
 (Aib^{8,30,35}, Lys²⁶(N^c-hexadecanoyl), Arg³⁴)hGLP-1(7-36)NH₂;
 (Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;

20 (Aib^{8,30,35}, Arg²⁶, Lys³⁴(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,30,35}, Arg^{26,34}, Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;

25 (Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, A6c³², Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

30 (Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^c-tetradecanoyl))hGLP-1(7-36)NH₂;
 (Aib^{8,24,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁶(N^c-hexadecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁸(N^ε-octanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁸(N^ε-tetradecanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,24,30,35}, Glu²³, Arg^{26,34}, A6c³², Lys³⁸(N^ε-hexadecanoyl))hGLP-1(7-36)NH₂;

((N^α-HEPES-His)⁷, Aib³⁵)hGLP-1(7-36)NH₂;

5 ((N^α-HEPES-His)⁷, β-Ala³⁵)hGLP-1(7-36)NH₂;

((N^α-HEPES-His)⁷, Aib⁸, β-Ala³⁵)hGLP-1(7-36)NH₂;

((N^α-HEPA-His)⁷, Aib³⁵)hGLP-1(7-36)NH₂;

((N^α-HEPA-His)⁷, β-Ala³⁵)hGLP-1(7-36)NH₂;

((N^α-HEPA-His)⁷, Aib⁸, β-Ala³⁵)hGLP-1(7-36)NH₂;

10 ((N^α-tetradecanoyl-His)⁷, Aib³⁵)hGLP-1(7-36)NH₂;

((N^α-tetradecanoyl-His)⁷, β-Ala³⁵)hGLP-1(7-36)NH₂;

((N^α-tetradecanoyl-His)⁷, Aib^{8,35})hGLP-1(7-36)NH₂;

((N^α-tetradecanoyl-His)⁷, Aib⁸, β-Ala³⁵)hGLP-1(7-36)NH₂;

((N^α-tetradecanoyl-His)⁷, Arg^{26,34}, Aib³⁵)hGLP-1(7-36)NH₂;

15 ((N^α-tetradecanoyl-His)⁷, Arg^{26,34}, β-Ala³⁵)hGLP-1(7-36)NH₂;

((N^α-tetradecanoyl-His)⁷, Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH₂;

((N^α-tetradecanoyl-His)⁷, Aib⁸, Arg^{26,34}, β-Ala³⁵)hGLP-1(7-36)NH₂;

((N^α-tetradecanoyl-His)⁷, Arg^{25,26,34}, β-Ala³⁵)hGLP-1(7-36)NH₂;

((N^α-tetradecanoyl-His)⁷, Aib^{8,35}, Arg^{25,26,34})hGLP-1(7-36)NH₂;

20 ((N^α-tetradecanoyl-His)⁷, Aib⁸, Arg^{25,26,34}, β-Ala³⁵)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Lys²⁶(N^ε-octanesulfonyl), Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Lys²⁶(N^ε-dodecanesulfonyl), Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Lys²⁶(N^ε-hexadecanesulfonyl), Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-octanesulfonyl))hGLP-1(7-36)NH₂;

25 (Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-dodecanesulfonyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg²⁶, Lys³⁴(N^ε-hexadecanesulfonyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-octanesulfonyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-hexadecanesulfonyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Asp²⁶(1-(4-decylpiperazine)), Arg³⁴)hGLP-1(7-36)NH₂;

30 (Aib^{8,35}, Asp²⁶(1-(4-dodecylpiperazine)), Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Asp²⁶(1-(4-tetradecylpiperazine)), Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Asp²⁶(1-(4-hexadecylpiperazine)), Arg³⁴)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-decylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁶, Asp³⁴(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH₂;

5 (Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH₂;

10 (Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg^{26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH₂;

15 (Aib^{8,35,37}, Arg^{26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-decylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,34}, Asp²⁶(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH₂;

20 (Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-decylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26}, Asp³⁴(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-decylpiperazine)))hGLP-1(7-36)NH₂;

25 (Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-dodecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-tetradecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26,34}, Asp³⁶(1-(4-hexadecylpiperazine)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH₂;

30 (Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg^{25,26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-decylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-dodecylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-tetradecylpiperazine)))hGLP-1(7-38)NH₂;

(Aib^{8,35,37}, Arg^{25,26,34}, Asp³⁸(1-(4-hexadecylpiperazine)))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg^{26,34}, Glu³⁸(1-dodecylamino))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Glu²⁸(1-dodecylamino), Arg³⁴)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁸, Glu³⁴(1-dodecylamino))hGLP-1(7-36)NH₂;

5 (Aib^{8,35,37}, Arg^{26,34}, Glu³⁸(1-dodecylamino))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg³⁴, Lys²⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg³⁴, Lys²⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;

10 (Aib^{8,35}, Arg²⁸, Lys³⁴(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁸, Lys³⁴(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁸, Lys³⁴(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg²⁸, Lys³⁴(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;

15 (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;

20 (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;
(Aib^{8,35,37}, Arg^{26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;

25 (Aib^{8,35}, Arg^{25,34}, Lys²⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,34}, Lys²⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,34}, Lys²⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
Aib^{8,35}, Arg^{25,34}, Lys²⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;

30 (Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{25,26}, Lys³⁴(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{25,26,34}, Lys³⁶(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-36)NH₂;

5 (Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;

(Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;

(Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;

(Aib^{8,35}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-decyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;

10 (Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-dodecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-tetradecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;

(Aib^{8,35,37}, Arg^{25,26,34}, Lys³⁸(N^ε-(2-(4-hexadecyl-1-piperazine)-acetyl)))hGLP-1(7-38)NH₂;

15 (Aib^{8,35}, Arg^{26,34}, Lys³⁸(N^ε-decanoyl))hGLP-1(7-36)OH;

(Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^ε-decanoyl))hGLP-1(7-36)OH;

(Aib^{8,35}, Arg^{26,34}, Ava³⁷, Ado³⁸)hGLP-1(7-38)NH₂;

(Aib^{8,35}, Arg^{26,34}, Asp³⁷, Ava³⁸, Ado³⁹)hGLP-1(7-39)NH₂;

(Aib^{8,35}, Arg^{26,34}, Aun³⁷)hGLP-1(7-37)NH₂;

20 (Aib^{8,17,35},)hGLP-1(7-36)NH₂;

(Aib⁸, Arg^{26,34}, β -Ala³⁵, D-Asp³⁷, Ava³⁸, Aun³⁹)hGLP-1(7-39)NH₂;

(Gly⁸, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Ser⁸, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Glu^{22,23}, β -Ala³⁵)hGLP-1(7-36)NH₂;

25 (Gly⁸, Aib³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Lys¹⁸, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Leu²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Lys³³, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Lys¹⁶, Leu²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂;

30 (Aib⁸, D-Arg³⁶)hGLP-1(7-36)NH₂;

(Aib⁸, β -Ala³⁵, D-Arg³⁷)hGLP-1(7-37)NH₂;

(Aib^{8,27}, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib^{8,27}, β -Ala^{35,37}, Arg³⁸)hGLP-1(7-38)NH₂;

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(Aib^{8,27}, β -Ala^{35,37}, Arg^{38,39})hGLP-1(7-39)NH₂;
(Aib⁸, Lys^{18,27}, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, Lys²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, β -Ala³⁵, Arg³⁸)hGLP-1(7-38)NH₂;

5 (Aib⁸, Arg^{26,34}, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, D-Arg³⁵)hGLP-1(7-36)NH₂;
(Aib⁸, β -Ala³⁵, Arg³⁷)hGLP-1(7-37)NH₂;
(Aib⁸, Phe³¹, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Phe³¹)hGLP-1(7-36)NH₂;

10 (Aib^{8,35}, Nal³¹)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Nal^{28,31})hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Nal³¹)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Phe³¹)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Nal^{19,31})hGLP-1(7-36)NH₂;

15 (Aib^{8,35}, Nal^{12,31})hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys³⁶(N^c-decanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg³⁴, Lys²⁶(N^c-decanoyl))hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-dodecanoyl))hGLP-1(7-36)NH₂;
(Aib⁸, β -Ala³⁵, Ser³⁷(O-decanoyl))hGLP1(7-37)-NH₂;

20 (Aib^{8,27}, β -Ala^{35,37}, Arg³⁸, Lys³⁹(N^c-octanoyl))hGLP-1(7-39)NH₂;
(Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-octanoyl))hGLP-1(7-37)NH₂;
(Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-decanoyl))hGLP-1(7-37)NH₂;
(Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-tetradecanoyl))hGLP-1(7-37)NH₂;

25 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-dodecanoyl))hGLP-1(7-37)NH₂; or
(Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-dodecanoyl))hGLP-1(8-37)NH₂;
or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 15 wherein said compound is

(Aib^{8,35}, A6c³²)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Glu²³)hGLP-1(7-36)NH₂;

30 (Aib^{8,24,35})hGLP-1(7-36)NH₂;
(Aib^{8,35}, Glu²³, A6c³²)hGLP-1(7-36)NH₂;
(Aib⁸, Glu²³, β -Ala³⁵)hGLP-1(7-36)NH₂;
(Aib^{8,35}, Arg^{26,34})hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-octanoyl))hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-decanoyl))hGLP-1(7-36)OH;

(Aib^{8,35}, Lys²⁵, Arg^{26,34}, Lys³⁶(N^c-decanoyl))hGLP-1(7-36)OH;

(Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁶(N^c-Aec-decanoyl))hGLP-1(7-36)NH₂;

5 (Aib^{8,35}, Arg^{26,34}, Ava³⁷, Ado³⁸)hGLP-1(7-38)NH₂;

(Aib^{8,35}, Arg^{26,34}, Asp³⁷, Ava³⁸, Ado³⁹)hGLP-1(7-39)NH₂;

(Aib^{8,35}, Arg^{26,34}, Aun³⁷)hGLP-1(7-37)NH₂;

(Aib^{8,17,35})hGLP-1(7-36)NH₂;

(Aib⁸, Arg^{26,34}, β -Ala³⁵, D-Asp³⁷, Ava³⁸, Aun³⁹)hGLP-1(7-39)NH₂;

10 (Gly⁸, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Ser⁸, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Glu^{22,23}, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Gly⁸, Aib³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Lys¹⁸, β -Ala³⁵)hGLP-1(7-36)NH₂;

15 (Aib⁸, Leu²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Lys³³, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Lys¹⁸, Leu²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, D-Arg³⁶)hGLP-1(7-36)NH₂;

(Aib⁸, β -Ala³⁵, D-Arg³⁷)hGLP-1(7-37)NH₂;

20 (Aib^{8,27}, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib^{8,27}, β -Ala^{35,37}, Arg³⁸)hGLP-1(7-38)NH₂;

(Aib^{8,27}, β -Ala^{35,37}, Arg^{38,39})hGLP-1(7-39)NH₂;

(Aib⁸, Lys^{18,27}, β -Ala³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, Lys²⁷, β -Ala³⁵)hGLP-1(7-36)NH₂;

25 (Aib⁸, β -Ala³⁵, Arg³⁸)hGLP-1(7-38)NH₂;

(Aib⁸, Arg^{26,34}, β -Ala³⁵,)hGLP-1(7-36)NH₂;

(Aib⁸, D-Arg³⁵)hGLP-1(7-36)NH₂;

(Aib⁸, β -Ala³⁵, Arg³⁷)hGLP-1(7-37)NH₂;

(Aib⁸, Phe³¹, β -Ala³⁵)hGLP-1(7-36)NH₂;

30 (Aib^{8,35}, Phe³¹)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Nal³¹)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Nal^{28,31})hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{26,34}, Nal³¹)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Arg^{26,34}, Phe³¹)hGLP-1(7-36)NH₂;

(Aib^{8,35}, Nal^{19,31})hGLP-1(7-36)NH₂;
(Aib^{8,35}, Nal^{12,31})hGLP-1(7-36)NH₂;
(Aib^{8,35}, Lys³⁶(N^c-decanoyl))hGLP-1(7-36) NH₂;
(Aib^{8,35}, Arg³⁴, Lys²⁶(N^c-decanoyl))hGLP-1(7-36)NH₂;
5 (Aib^{8,35}, Arg^{26,34}, Lys³⁶(N^c-dodecanoyl))hGLP-1(7-36)NH₂;
(Aib⁸, B-Ala³⁵, Ser³⁷(O-decanoyl))hGLP1(7-37)-NH₂;
(Aib^{8,27}, β -Ala^{35,37}, Arg³⁸, Lys³⁹(N^c-octanoyl))hGLP-1(7-39)NH₂;
(Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-octanoyl))hGLP-1(7-37)NH₂;
10 (Aib⁸, Arg^{26,34}, β -Ala³⁵, Lys³⁷(N^c-decanoyl))hGLP-1(7-37)NH₂;
or a pharmaceutically acceptable salt thereof.

17. Use of a compound as claimed in any of claims 1 to 10, or 15 or 16, in the preparation of a medicament for the treatment of disease.

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18. Use as claimed in claim 17, in which the disease is selected from the group consisting of Type I diabetes, Type II diabetes, obesity, glucagonomas, secretory disorders of the airway, metabolic disorder, arthritis, osteoporosis, central nervous system disease, restenosis and neurodegenerative disease.